NEUROSCIENCE

Third Edition

NEUROSCIENCE THIRD EDITION

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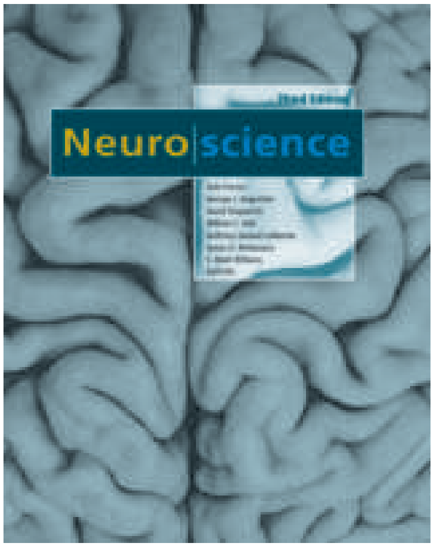

THE COVER
Dorsal view of the human brain.
(Courtesy of S. Mark Williams.)

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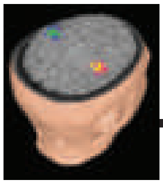

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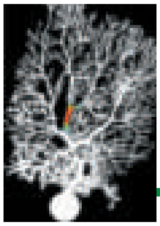

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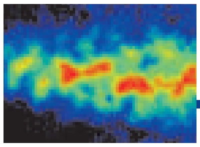

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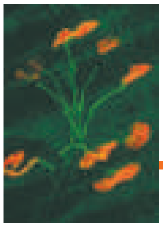

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Preface

Whether judged in molecular, cellular, systemic, behavioral, or cognitive terms, the human nervous system is a stupendous piece of biological machinery. Given its accomplishments—all the artifacts of human culture, for instance—there is good reason for wanting to understand how the brain and the rest of the nervous system works. The debilitating and costly effects of neurological and psychiatric disease add a further sense of urgency to this quest. The aim of this book is to highlight the intellectual challenges and excitement—as well as the uncertainties—of what many see as the last great frontier of biological science. The information presented should serve as a starting point for undergraduates, medical students, graduate students in the neurosciences, and others who want to understand how the human nervous system operates. Like any other great challenge, neuroscience should be, and is, full of debate, dissension, and considerable fun. All these ingredients have gone into the construction of the third edition of this book; we hope they will be conveyed in equal measure to readers at all levels.

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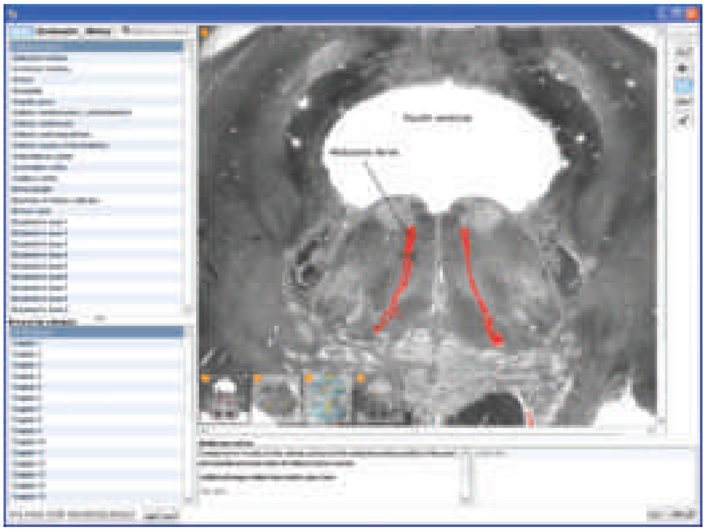
We also thank the students at Duke University Medical School as well as many other students and colleagues who provided suggestions for improvement of the last edition. Finally, we owe special thanks to Robert Reynolds and Nate O'Keefe, who labored long and hard to put the third edition together, and to Andy Sinauer, Graig Donini, Carol Wigg, Christopher Small, Janice Holabird, and the rest of the staff at Sinauer Associates for their outstanding work and high standards.

Supplements to Accompany NEUROSCIENCE Third Edition

For the Student

Sylvius for Neuroscience:
A Visual Glossary of Human Neuroanatomy (CD-ROM)
S. Mark Williams, Leonard E. White, and Andrew C. Mace

Sylvius for Neuroscience: A Visual Glossary of Human Neuroanatomy, included in every copy of the textbook, is an interactive CD reference guide to the structure of the human nervous system. By entering a corresponding page number from the textbook, students can quickly search the CD for any neuroanatomical structure or term and view corresponding images and animations. Descriptive information is provided with all images and animations. Additionally, students can take notes on the content and share these with other *Sylvius* users. *Sylvius* is an essential study aid for learning basic human neuroanatomy.



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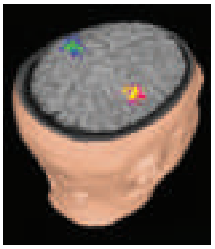
Chapter 1



Studying the Nervous Systems of Humans and Other Animals

Overview

Neuroscience encompasses a broad range of questions about how nervous systems are organized, and how they function to generate behavior. These questions can be explored using the analytical tools of genetics, molecular and cell biology, systems anatomy and physiology, behavioral biology, and psychology. The major challenge for a student of neuroscience is to integrate the diverse knowledge derived from these various levels of analysis into a more or less coherent understanding of brain structure and function (one has to qualify this statement because so many questions remain unanswered). Many of the issues that have been explored successfully concern how the principal cells of any nervous system—neurons and glia—perform their basic functions in anatomical, electrophysiological, and molecular terms. The varieties of neurons and supporting glial cells that have been identified are assembled into ensembles called neural circuits, and these circuits are the primary components of neural systems that process specific types of information. Neural systems comprise neurons and circuits in a number of discrete anatomical locations in the brain. These systems subserve one of three general functions. Sensory systems represent information about the state of the organism and its environment, motor systems organize and generate actions; and associational systems link the sensory and motor sides of the nervous system, providing the basis for "higher-order" functions such as perception, attention, cognition, emotions, rational thinking, and other complex brain functions that lie at the core of understanding human beings, their history and their future.

Genetics, Genomics, and the Brain

The recently completed sequencing of the genome in humans, mice, the fruit fly *Drosophila melanogaster*, and the nematode worm *Caenorhabditis elegans* is perhaps the logical starting point for studying the brain and the rest of the nervous system; after all, this inherited information is also the starting point of each individual organism. The relative ease of obtaining, analyzing, and correlating gene sequences with neurobiological observations has facilitated a wealth of new insights into the basic biology of the nervous system. In parallel with studies of normal nervous systems, the genetic analysis of human pedigrees with various brain diseases has led to a widespread sense that it will soon be possible to understand and treat disorders long considered beyond the reach of science and medicine.

A gene consists of DNA sequences called **exons** that are transcribed into a messenger RNA and subsequently a protein. The set of exons that defines

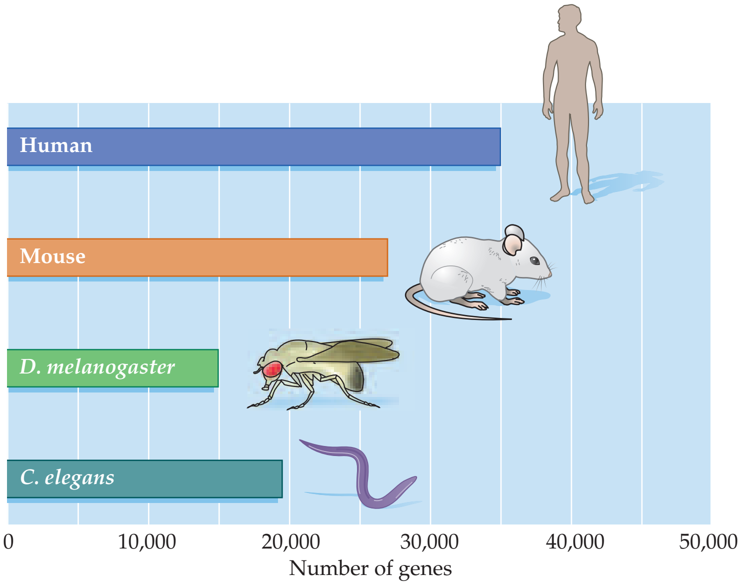


Figure 1.1 Estimates of the number of genes in the human genome, as well as in the genomes of the mouse, the fruit fly *Drosophila melanogaster*, and the nematode worm *Caenorhabditis elegans*.

the transcript of any gene is flanked by upstream (or 5′) and downstream (or 3′) regulatory sequences that control gene expression. In addition, sequences between exons—called **introns**—further influence transcription. Of the approximately 35,000 genes in the human genome, a majority are expressed in the developing and adult brain; the same is true in mice, flies, and worms—the species commonly used in modern genetics (and increasingly in neuroscience) (Figure 1.1). Nevertheless, very few genes are *uniquely* expressed in neurons, indicating that nerve cells share most of the basic structural and functional properties of other cells. Accordingly, most "brain-specific" genetic information must reside in the remainder of nucleic acid sequences—regulatory sequences and introns—that control the timing, quantity, variability and cellular specificity of gene expression.

One of the most promising dividends of sequencing the human genome has been the realization that one or a few genes, when altered (mutated), can begin to explain some aspects of neurological and psychiatric diseases. Before the "postgenomic era" (which began following completion of the sequencing of the human genome), many of the most devastating brain diseases remained largely mysterious because there was little sense of how or why the normal biology of the nervous system was compromised. The identification of genes correlated with disorders such as Huntington's disease, Parkinson's disease, Alzheimer's disease, major depression, and schizophrenia has provided a promising start to understanding these pathological processes in a much deeper way (and thus devising rational therapies).

Genetic and genomic information alone do not completely explain how the brain normally works or how disease processes disrupt its function. To achieve these goals it is equally essential to understand the cell biology, anatomy, and physiology of the brain in health as well as disease.

The Cellular Components of the Nervous System

Early in the nineteenth century, the cell was recognized as the fundamental unit of all living organisms. It was not until well into the twentieth century, however, that neuroscientists agreed that nervous tissue, like all other organs, is made up of these fundamental units. The major reason was that the first generation of "modern" neurobiologists in the nineteenth century had difficulty resolving the unitary nature of nerve cells with the microscopes and cell staining techniques that were then available. This inade-

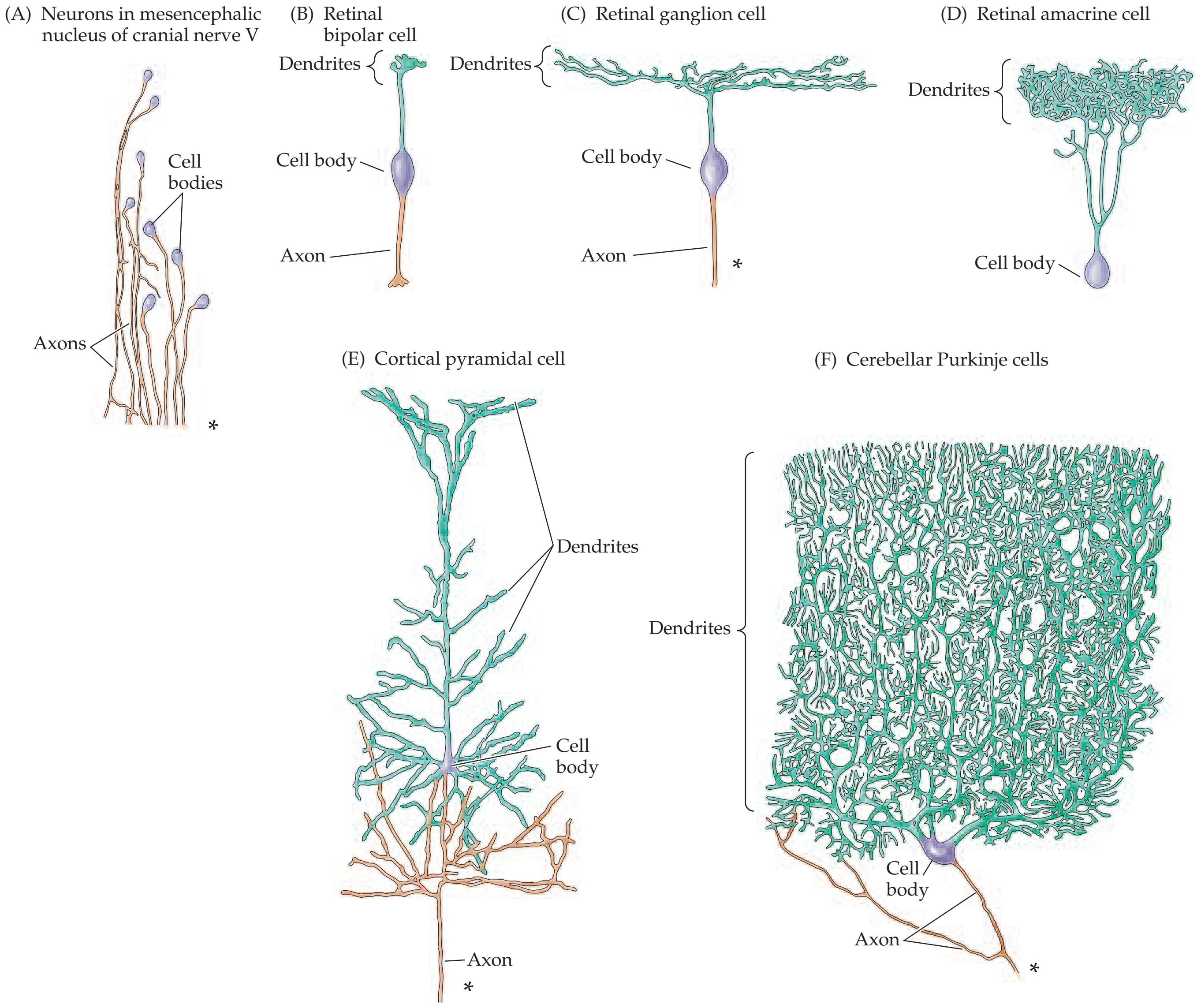

(A) Neurons in mesencephalic nucleus of cranial nerve V
Cell bodies
Axons
*
(B) Retinal bipolar cell
Dendrites
Cell body
Axon
(C) Retinal ganglion cell
Dendrites
Cell body
Axon
*
(D) Retinal amacrine cell
Dendrites
Cell body
(E) Cortical pyramidal cell
Dendrites
Cell body
Axon
*
(F) Cerebellar Purkinje cells
Dendrites
Cell body
Axon
*

Figure 1.2 Examples of the rich variety of nerve cell morphologies found in the human nervous system. Tracings are from actual nerve cells stained by impregnation with silver salts (the so-called Golgi technique, the method used in the classical studies of Golgi and Cajal). Asterisks indicate that the axon runs on much farther than shown. Note that some cells, like the retinal bipolar cell, have a very short axon, and that others, like the retinal amacrine cell, have no axon at all. The drawings are not all at the same scale.

quacy was exacerbated by the extraordinarily complex shapes and extensive branches of individual nerve cells, which further obscured their resemblance to the geometrically simpler cells of other tissues (Figures 1.2–1.4). As a result, some biologists of that era concluded that each nerve cell was connected to its neighbors by protoplasmic links, forming a continuous nerve cell network, or *reticulum*. The "reticular theory" of nerve cell communication, which was championed by the Italian neuropathologist Camillo Golgi (for whom the Golgi apparatus in cells is named), eventually fell from favor and was replaced by what came to be known as the "neuron doctrine." The major proponents of this new perspective were the Spanish neuroanatomist Santiago Ramón y Cajal and the British physiologist Charles Sherrington.

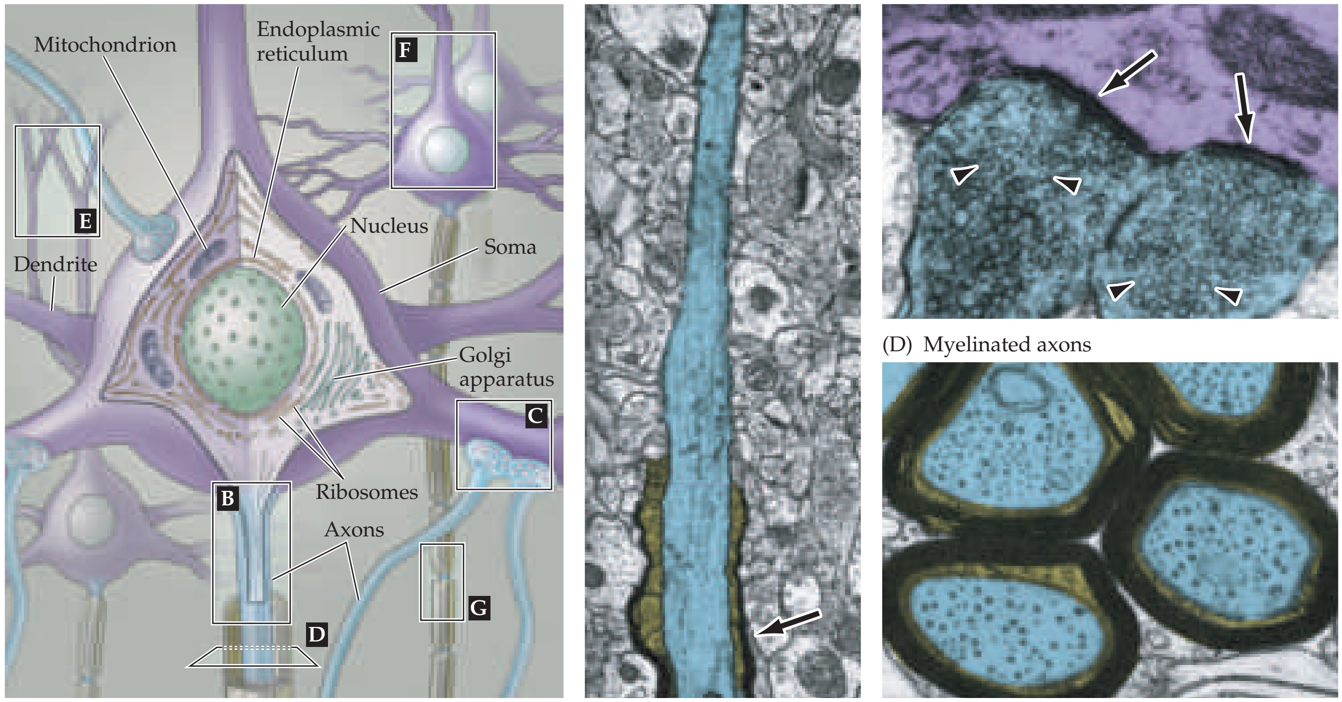
The contrasting views represented by Golgi and Cajal occasioned a spirited debate in the early twentieth century that set the course of modern neuroscience. Based on light microscopic examination of nervous tissue stained with silver salts according to a method pioneered by Golgi, Cajal argued persuasively that nerve cells are discrete entities, and that they communicate with one another by means of specialized contacts that Sherrington called "synapses." The work that framed this debate was recognized by the award of the Nobel Prize for Physiology or Medicine in 1906 to both Golgi and Cajal (the joint award suggests some ongoing concern about just who was correct, despite Cajal's overwhelming evidence). The subsequent work of Sherrington and others demonstrating the transfer of electrical signals at synaptic junctions between nerve cells provided strong support of the "neuron doctrine," but challenges to the autonomy of individual neurons remained. It was not until the advent of electron microscopy in the 1950s that any lingering doubts about the discreteness of neurons were resolved. The high-magnification, high-resolution pictures that could be obtained with the electron microscope clearly established that nerve cells are functionally independent units; such pictures also identified the specialized cellular junctions that Sherrington had named synapses (see Figures 1.3 and 1.4).

The histological studies of Cajal, Golgi, and a host of successors led to the further consensus that the cells of the nervous system can be divided into two broad categories: **nerve cells** (or **neurons**), and supporting cells called **neuroglia** (or simply **glia**; see Figure 1.5). Nerve cells are specialized for electrical signaling over long distances, and understanding this process represents one of the more dramatic success stories in modern biology (and the subject of Unit I of this book). Supporting cells, in contrast, are not capable of electrical signaling; nevertheless, they have several essential functions in the developing and adult brain.

Neurons

Neurons and glia share the complement of organelles found in all cells, including the endoplasmic reticulum and Golgi apparatus, mitochondria, and a variety of vesicular structures. In neurons, however, these organelles are often more prominent in distinct regions of the cell. In addition to the distribution of organelles and subcellular components, neurons and glia are in some measure different from other cells in the specialized fibrillar or tubular proteins that constitute the cytoskeleton (Figures 1.3 and 1.4). Although many of these proteins—isoforms of actin, tubulin, and myosin, as well as several others—are found in other cells, their distinctive organization in neurons is critical for the stability and function of neuronal processes and synaptic junctions. The filaments, tubules, vesicular motors, and scaffolding proteins of neurons orchestrate the growth of axons and dendrites; the trafficking and appropiate positioning of membrane components, organelles, and vesicles; and the active processes of exocytosis and endocytosis that underlie synaptic communication. Understanding the ways in which these molecular components are used to insure the proper development and function of neurons and glia remains a primary focus of modern neurobiology.

The basic cellular organization of neurons resembles that of other cells; however, they are clearly distinguished by specialization for intercellular communication. This attribute is apparent in their overall morphology, in the specific organization of their membrane components for electrical signaling, and in the structural and functional intricacies of the synaptic contacts between neurons (see Figures 1.3 and 1.4). The most obvious sign of neuronal specialization for communication via electrical signaling is the extensive branching of neurons. The most salient aspect of this branching for typical nerve cells is the elaborate arborization of **dendrites** that arise from the neuronal cell body (also called *dendritic branches* or *dendritic processes*). Dendrites are the primary target for synaptic input from other neurons and are


(A)

(B) Axon

(C) Synaptic endings (terminal boutons)

(D) Myelinated axons

Mitochondrion
Endoplasmic reticulum
F
E
Nucleus
Soma
Dendrite
Golgi apparatus
C
B
Ribosomes
Axons
G
D

(E) Dendrites

(F) Neuronal cell body (soma)

(G) Myelinated axon and node of Ranvier

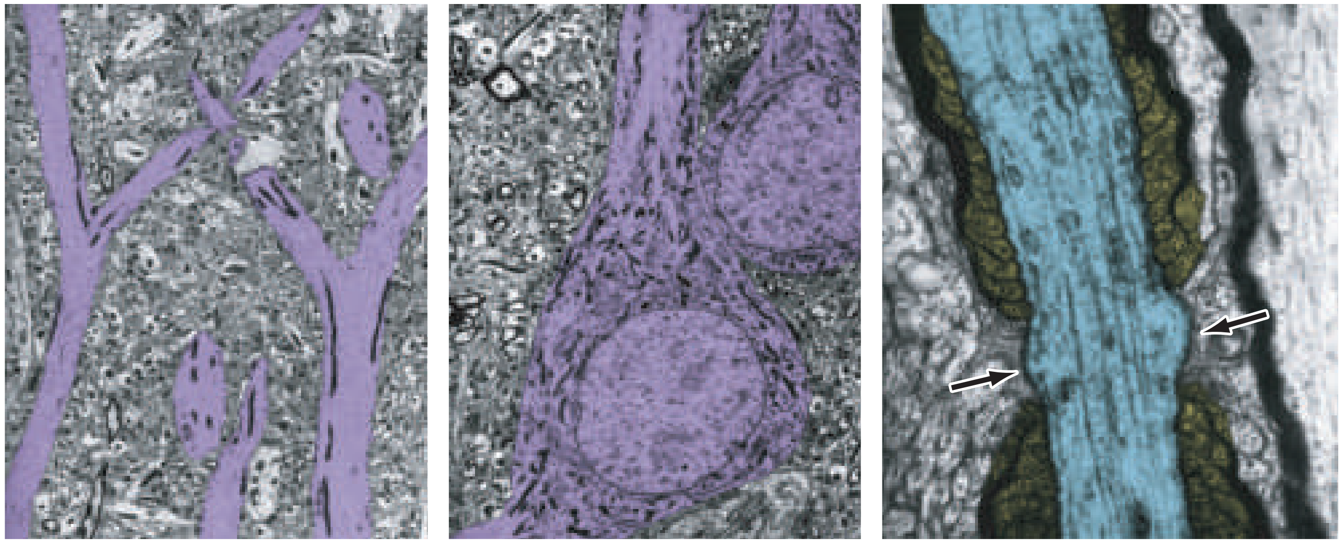


Figure 1.3 The major light and electron microscopical features of neurons. (A) Diagram of nerve cells and their component parts. (B) Axon initial segment (blue) entering a myelin sheath (gold). (C) Terminal boutons (blue) loaded with synaptic vesicles (arrowheads) forming synapses (arrows) with a dendrite (purple). (D) Transverse section of axons (blue) ensheathed by the processes of oligodendrocytes (gold). (E) Apical dendrites (purple) of cortical pyramidal cells. (F) Nerve cell bodies (purple) occupied by large round nuclei. (G) Portion of a myelinated axon (blue) illustrating the intervals between adjacent segments of myelin (gold) referred to as nodes of Ranvier (arrows). (Micrographs from Peters et al., 1991.)

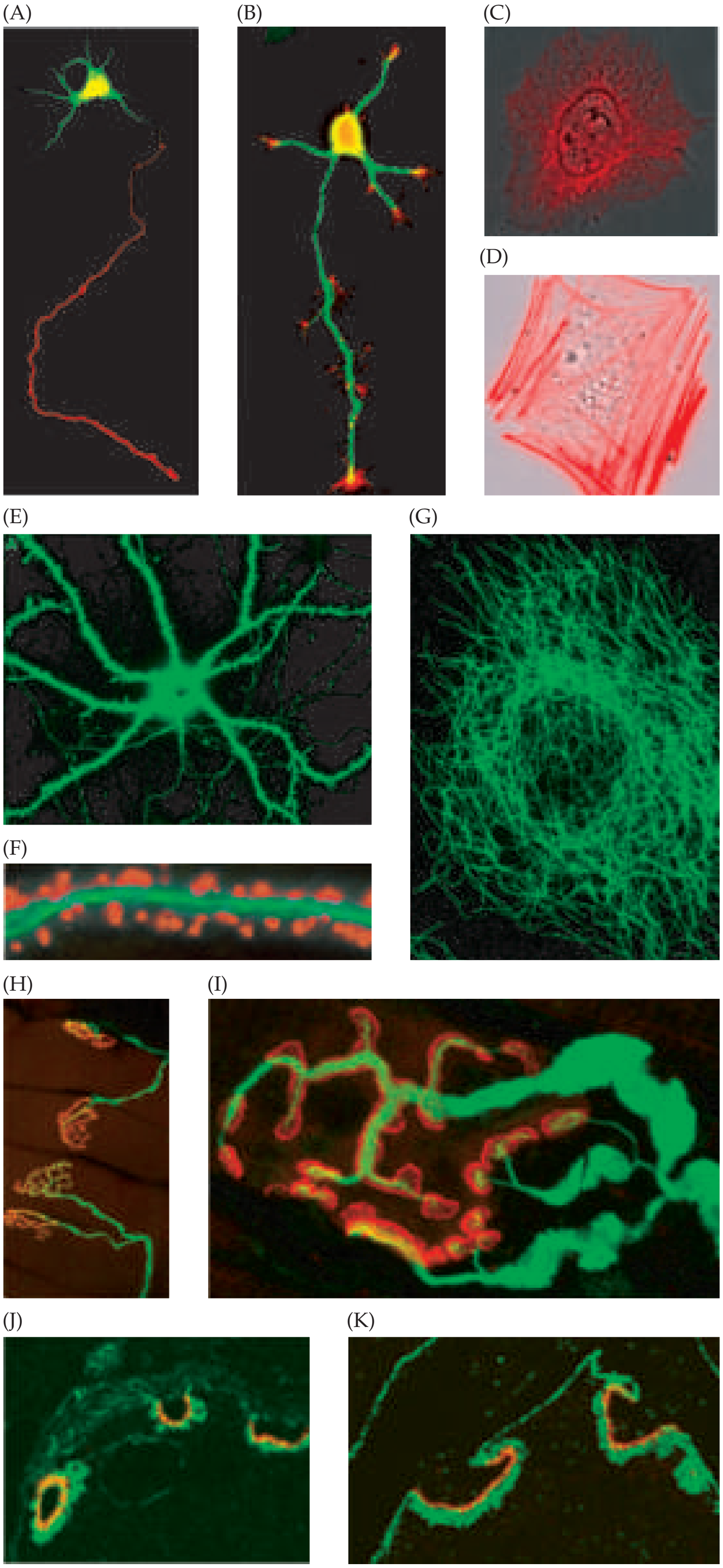


Figure 1.4 Distinctive arrangement of cytoskeletal elements in neurons. (A) The cell body, axons, and dendrites are distinguished by the distribution of tubulin (green throughout cell) versus other cytoskeletal elements—in this case, Tau (red), a microtubule-binding protein found only in axons. (B) The strikingly distinct localization of actin (red) to the growing tips of axonal and dendritic processes is shown here in cultured neuron taken from the hippocampus. (C) In contrast, in a cultured epithelial cell, actin (red) is distributed in fibrils that occupy most of the cell body. (D) In astroglial cells in culture, actin (red) is also seen in fibrillar bundles. (E) Tubulin (green) is seen throughout the cell body and dendrites of neurons. (F) Although tubulin is a major component of dendrites, extending into spines, the head of the spine is enriched in actin (red). (G) The tubulin component of the cytoskeleton in non-neuronal cells is arrayed in filamentous networks. (H–K) Synapses have a distinct arrangement of cytoskeletal elements, receptors, and scaffold proteins. (H) Two axons (green; tubulin) from motor neurons are seen issuing two branches each to four muscle fibers. The red shows the clustering of postsynaptic receptors (in this case for the neurotransmitter acetylcholine). (I) A higher power view of a single motor neuron synapse shows the relationship between the axon (green) and the postsynaptic receptors (red). (J) The extracellular space between the axon and its target muscle is shown in green. (K) The clustering of scaffolding proteins (in this case, dystrophin) that localize receptors and link them to other cytoskeletal elements is shown in green. (A courtesy of Y. N. Jan; B courtesy of E. Dent and F. Gertler; C courtesy of D. Arneman and C. Otey; D courtesy of A. Gonzales and R. Cheney; E from Sheng, 2003; F from Matus, 2000; G courtesy of T. Salmon et al.; H–K courtesy of R. Sealock.)

also distinguished by their high content of ribosomes as well as specific cytoskeletal proteins that reflect their function in receiving and integrating information from other neurons. The spectrum of neuronal geometries ranges from a small minority of cells that lack dendrites altogether to neurons with dendritic arborizations that rival the complexity of a mature tree (see Figure 1.2). The number of inputs that a particular neuron receives depends on the complexity of its dendritic arbor: nerve cells that lack dendrites are innervated by (thus, receive electrical signals from) just one or a few other nerve cells, whereas those with increasingly elaborate dendrites are innervated by a commensurately larger number of other neurons.

The synaptic contacts made on dendrites (and, less frequently, on neuronal cell bodies) comprise a special elaboration of the secretory apparatus found in most polarized epithelial cells. Typically, the **presynaptic terminal** is immediately adjacent to a **postsynaptic specialization** of the target cell (see Figure 1.3). For the majority of synapses, there is no physical continuity between these pre- and postsynaptic elements. Instead, pre- and postsynaptic components communicate via secretion of molecules from the presynaptic terminal that bind to receptors in the postsynaptic specialization. These molecules must traverse an interval of extracellular space between pre- and postsynaptic elements called the **synaptic cleft**. The synaptic cleft, however, is not simply a space to be traversed; rather, it is the site of extracellular proteins that influence the diffusion, binding, and degradation of molecules secreted by the presynaptic terminal (see Figure 1.4). The number of synaptic inputs received by each nerve cell in the human nervous system varies from 1 to about 100,000. This range reflects a fundamental purpose of nerve cells, namely to integrate information from other neurons. The number of synaptic contacts from different presynaptic neurons onto any particular cell is therefore an especially important determinant of neuronal function.

The information conveyed by synapses on the neuronal dendrites is integrated and "read out" at the origin of the **axon**, the portion of the nerve cell specialized for signal conduction to the next site of synaptic interaction (see Figures 1.2 and 1.3). The axon is a unique extension from the neuronal cell body that may travel a few hundred micrometers (μm; usually called microns) or much farther, depending on the type of neuron and the size of the species. Moreover, the axon also has a distinct cytoskeleton whose elements are central for its functional integrity (see Figure 1.4). Many nerve cells in the human brain (as well as that of other species) have axons no more than a few millimeters long, and a few have no axons at all.

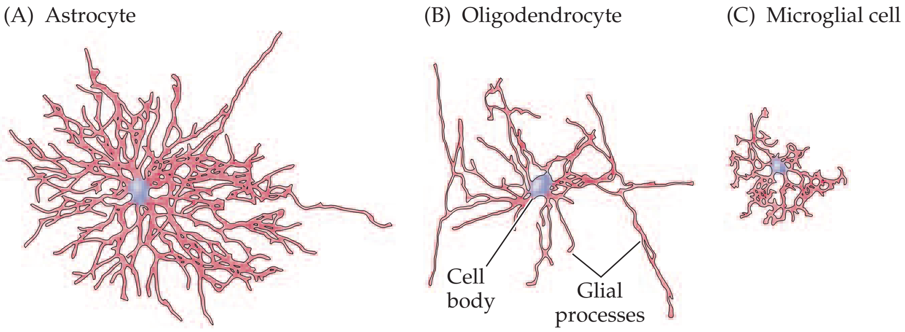
Relatively short axons are a feature of **local circuit neurons** or **interneurons** throughout the brain. The axons of projection neurons, however, extend to distant targets. For example, the axons that run from the human spinal cord to the foot are about a meter long. The electrical event that carries signals over such distances is called the **action potential**, which is a self-regenerating wave of electrical activity that propagates from its point of initiation at the cell body (called the **axon hillock**) to the terminus of the axon where synaptic contacts are made. The target cells of neurons include other nerve cells in the brain, spinal cord, and autonomic ganglia, and the cells of muscles and glands throughout the body.

The chemical and electrical process by which the information encoded by action potentials is passed on at synaptic contacts to the next cell in a pathway is called **synaptic transmission**. Presynaptic terminals (also called *synaptic endings*, *axon terminals*, or *terminal boutons*) and their postsynaptic specializations are typically **chemical synapses**, the most abundant type of synapse in the nervous system. Another type, the electrical synapse, is far more rare (see Chapter 5). The secretory organelles in the presynaptic terminal of chemical synapses are **synaptic vesicles** (see Figure 1.3), which are generally spherical structures filled with **neurotransmitter** molecules. The positioning of synaptic vesicles at the presynaptic membrane and their fusion to initiate neurotransmitter release is regulated by a number of proteins either within or associated with the vesicle. The neurotransmitters released from synaptic vesicles modify the electrical properties of the target cell by binding to **neurotransmitter receptors** (Figure 1.4), which are localized primarily at the postsynaptic specialization.

The intricate and concerted activity of neurotransmitters, receptors, related cytoskeletal elements, and signal transduction molecules are thus the basis for nerve cells communicating with one another, and with effector cells in muscles and glands.

Neuroglial Cells

Neuroglial cells—also referred to as glial cells or simply glia—are quite different from nerve cells. Glia are more numerous than neurons in the brain, outnumbering them by a ratio of perhaps 3 to 1. The major distinction is that glia do not participate directly in synaptic interactions and electrical signaling, although their supportive functions help define synaptic contacts and maintain the signaling abilities of neurons. Although glial cells also have complex processes extending from their cell bodies, these are generally less prominent than neuronal branches, and do not serve the same purposes as axons and dendrites (Figure 1.5).



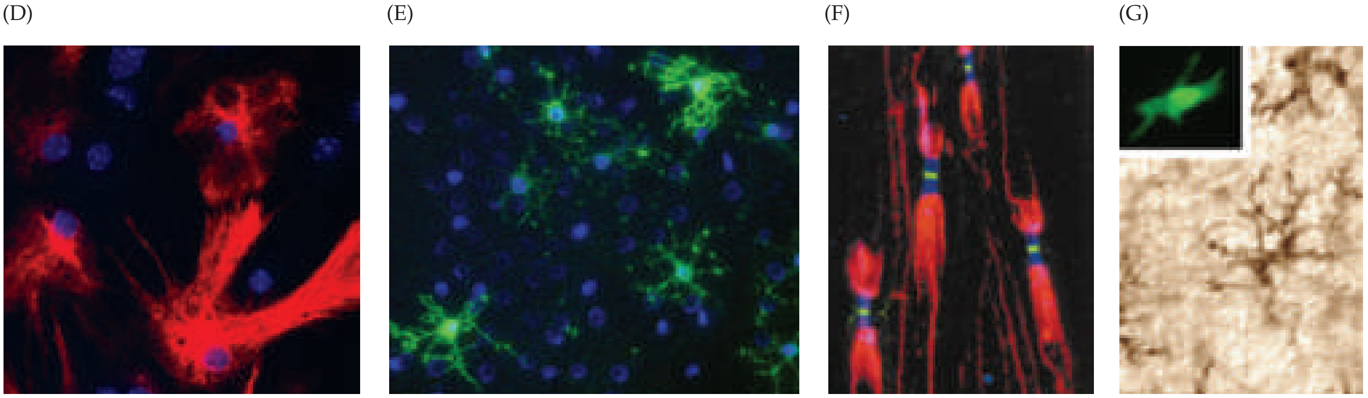


Figure 1.5 Varieties of neuroglial cells. Tracings of an astrocyte (A), an oligodendrocyte (B), and a microglial cell (C) visualized using the Golgi method. The images are at approximately the same scale. (D) Astrocytes in tissue culture, labeled (red) with an antibody against an astrocyte-specific protein. (E) Oligodendroglial cells in tissue culture labeled with an antibody against an oligodendroglial-specific protein. (F) Peripheral axon are ensheathed by myelin (labeled red) except at a distinct region called the node of Ranvier. The green label indicates ion channels concentrated in the node; the blue label indicates a molecularly distinct region called the paranode. (G) Microglial cells from the spinal cord, labeled with a cell type-specific antibody. Inset: Higher-magnification image of a single microglial cell labeled with a macrophage-selective marker. (A–C after Jones and Cowan, 1983; D, E courtesy of A.-S. LaMantia; F courtesy of M. Bhat; G courtesy of A. Light; inset courtesy of G. Matsushima.)

The term *glia* (from the Greek word meaning "glue") reflects the nineteenth-century presumption that these cells held the nervous system together in some way. The word has survived, despite the lack of any evidence that binding nerve cells together is among the many functions of glial cells. Glial roles that *are* well-established include maintaining the ionic milieu of nerve cells, modulating the rate of nerve signal propagation, modulating synaptic action by controlling the uptake of neurotransmitters at or near the synaptic cleft, providing a scaffold for some aspects of neural development, and aiding in (or impeding, in some instances) recovery from neural injury.

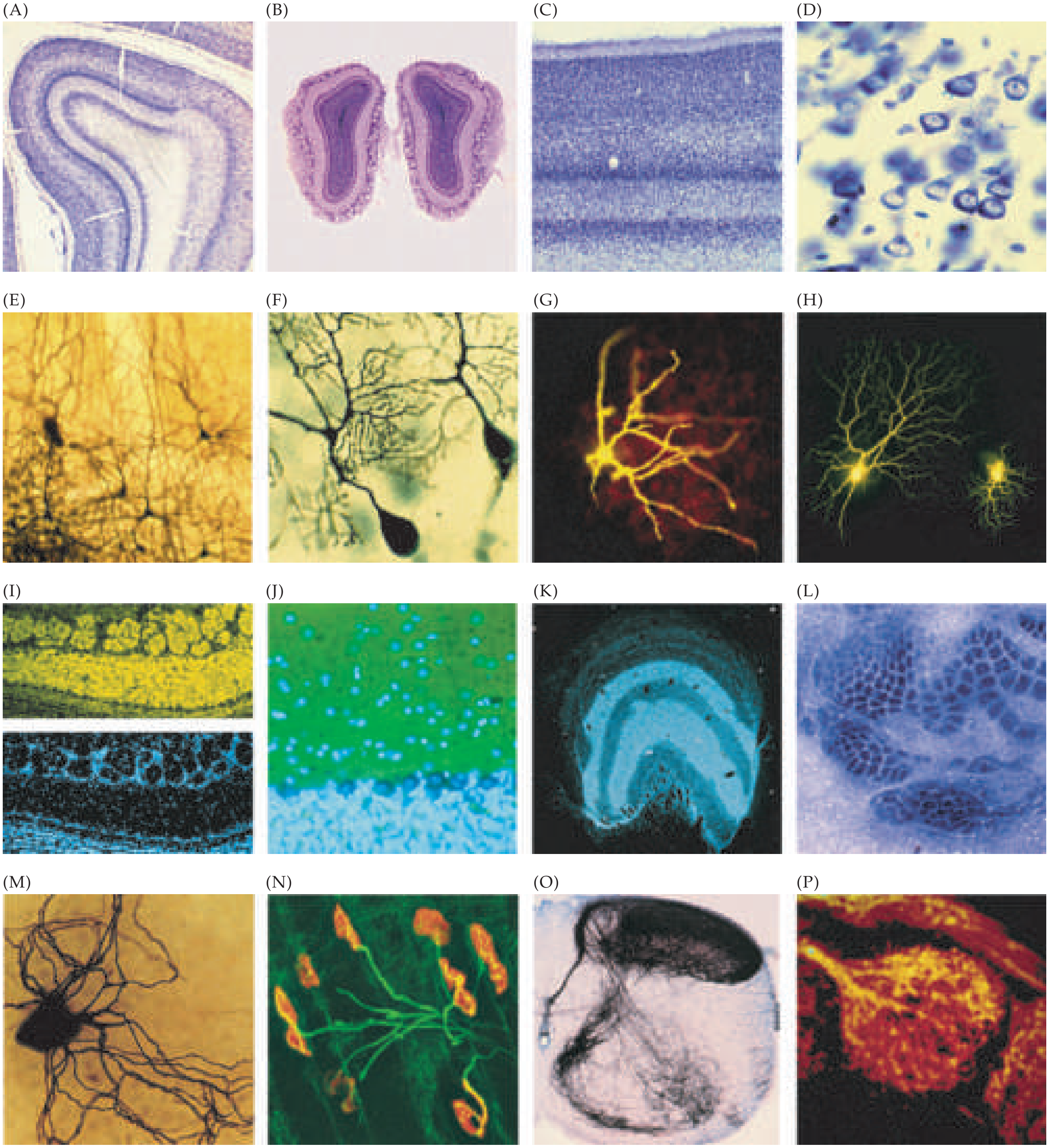
There are three types of glial cells in the mature central nervous system: astrocytes, oligodendrocytes, and microglial cells (see Figure 1.5). **Astrocytes**, which are restricted to the brain and spinal cord, have elaborate local processes that give these cells a starlike appearance (hence the prefix "astro"). A major function of astrocytes is to maintain, in a variety of ways, an appropriate chemical environment for neuronal signaling. **Oligodendrocytes**, which are also restricted to the central nervous system, lay down a laminated, lipid-rich wrapping called **myelin** around some, but not all, axons. Myelin has important effects on the speed of the transmission of electrical signals (see Chapter 3). In the peripheral nervous system, the cells that elaborate myelin are called **Schwann cells**.

Finally, **microglial cells** are derived primarily from hematopoietic precursor cells (although some may be derived directly from neural precursor cells). They share many properties with macrophages found in other tissues, and are primarily scavenger cells that remove cellular debris from sites of injury or normal cell turnover. In addition, microglia, like their macrophage counterparts, secrete signaling molecules—particularly a wide range of cytokines that are also produced by cells of the immune system—that can modulate local inflammation and influence cell survival or death. Indeed, some neurobiologists prefer to categorize microglia as a type of macrophage. Following brain damage, the number of microglia at the site of injury increases dramatically. Some of these cells proliferate from microglia resident in the brain, while others come from macrophages that migrate to the injured area and enter the brain via local disruptions in the cerebral vasculature.

Cellular Diversity in the Nervous System

Although the cellular constituents of the human nervous system are in many ways similar to those of other organs, they are unusual in their extraordinary numbers: the human brain is estimated to contain 100 billion neurons and several times as many supporting cells. More importantly, the nervous system has a greater range of distinct cell types—whether categorized by morphology, molecular identity, or physiological activity—than any other organ system (a fact that presumably explains why so many different genes are expressed in the nervous system; see above). The cellular diversity of any nervous system—including our own—undoubtedly underlies the the capacity of the system to form increasingly complicated networks to mediate increasingly sophisticated behaviors.

For much of the twentieth century, neuroscientists relied on the same set of techniques developed by Cajal and Golgi to describe and categorize the diversity of cell types in the nervous system. From the late 1970s onward, however, new technologies made possible by the advances in cell and molecular biology provided investigators with many additional tools to discern the properties of neurons (Figure 1.6). Whereas general cell staining methods



showed mainly differences in cell size and distribution, antibody stains and probes for messenger RNA added greatly to the appreciation of distinctive types of neurons and glia in various regions of the nervous system. At the same time, new tract tracing methods using a wide variety of tracing substances allowed the interconnections among specific groups of neurons to be

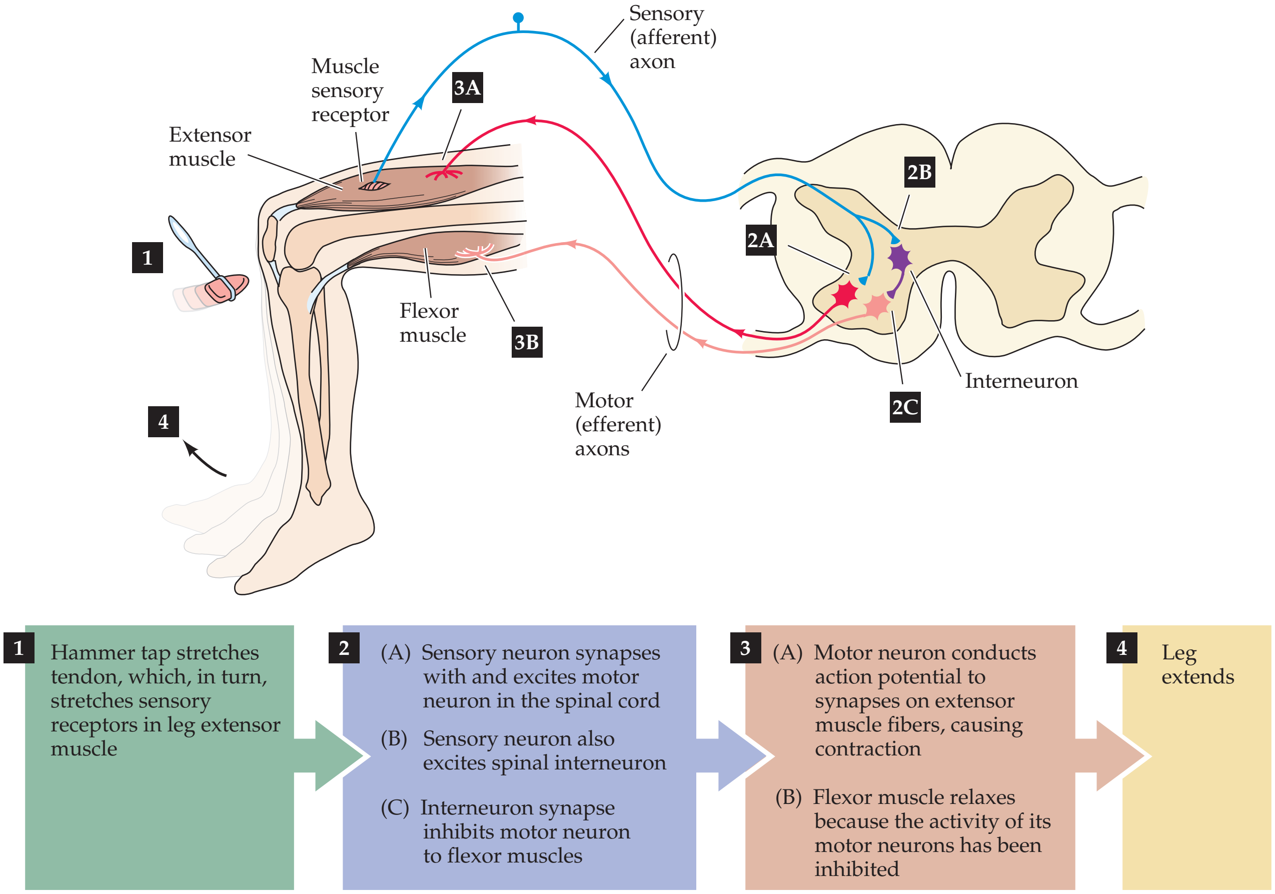
◀ **Figure 1.6** Structural diversity in the nervous system demonstrated with cellular and molecular markers. *First row:* Cellular organization of different brain regions demonstrated with Nissl stains, which label nerve and glial cell bodies. (A) The cerebral cortex at the boundary between the primary and secondary visual areas. (B) The olfactory bulbs. (C) Differences in cell density in cerebral cortical layers. (D) Individual Nissl-stained neurons and glia at higher magnification. *Second row:* Classical and modern approaches to seeing individual neurons and their processes. (E) Golgi-labeled cortical pyramidal cells. (F) Golgi-labeled cerebellar Purkinje cells. (G) Cortical interneuron labeled by intracellular injection of a fluorescent dye. (H) Retinal neurons labeled by intracellular injection of fluorescent dye. *Third row:* Cellular and molecular approaches to seeing neural connections and systems. (I) At top, an antibody that detects synaptic proteins in the olfactory bulb; at bottom, a fluorescent label shows the location of cell bodies. (J) Synaptic zones and the location of Purkinje cell bodies in the cerebellar cortex labeled with synapse-specific antibodies (green) and a cell body marker (blue). (K) The projection from one eye to the lateral geniculate nucleus in the thalamus, traced with radioactive amino acids (the bright label shows the axon terminals from the eye in distinct layers of the nucleus). (L) The map of the body surface of a rat in the somatic sensory cortex, shown with a marker that distinguishes zones of higher synapse density and metabolic activity. *Fourth row:* Peripheral neurons and their projections. (M) An autonomic neuron labeled by intracellular injection of an enzyme marker. (N) Motor axons (green) and neuromuscular synapses (orange) in transgenic mice genetically engineered to express fluorescent proteins. (O) The projection of dorsal root ganglia to the spinal cord, demonstrated by an enzymatic tracer. (P) Axons of olfactory receptor neurons from the nose labeled in the olfactory bulb with a vital fluorescent dye. (G courtesy of L. C. Katz; H courtesy of C. J. Shatz; N,O courtesy of W. Snider and J. Lichtman; all others courtesy of A.-S. LaMantia and D. Purves.)

explored much more fully. Tracers can be introduced into either living or fixed tissue, and are transported along nerve cell processes to reveal their origin and termination. More recently, genetic and neuroanatomical methods have been combined to visualize the expression of fluorescent or other tracer molecules under the control of regulatory sequences of neural genes. This approach, which shows individual cells in fixed or living tissue in remarkable detail, allows nerve cells to be identified by both their transcriptional state and their structure. Finally, ways of determining the molecular identity and morphology of nerve cells can be combined with measurements of their physiological activity, thus illuminating structure–function relationships. Examples of these various approaches are shown in Figure 1.6.

Neural Circuits

Neurons never function in isolation; they are organized into ensembles or **neural circuits** that process specific kinds of information and provide the foundation of sensation, perception and behavior. The synaptic connections that define such circuits are typically made in a dense tangle of dendrites, axons terminals, and glial cell processes that together constitute what is called **neuropil** (the suffix *-pil* comes from the Greek word *pilos*, meaning "felt"; see Figure 1.3). The neuropil is thus the region between nerve cell bodies where most synaptic connectivity occurs.

Although the arrangement of neural circuits varies greatly according to the function being served, some features are characteristic of all such ensembles. Preeminent is the direction of information flow in any particular circuit, which is obviously essential to understanding its purpose. Nerve cells that



1 Hammer tap stretches tendon, which, in turn, stretches sensory receptors in leg extensor muscle

2 (A) Sensory neuron synapses with and excites motor neuron in the spinal cord

(B) Sensory neuron also excites spinal interneuron

(C) Interneuron synapse inhibits motor neuron to flexor muscles

3 (A) Motor neuron conducts action potential to synapses on extensor muscle fibers, causing contraction

(B) Flexor muscle relaxes because the activity of its motor neurons has been inhibited

4 Leg extends

Figure 1.7 A simple reflex circuit, the knee-jerk response (more formally, the myotatic reflex), illustrates several points about the functional organization of neural circuits. Stimulation of peripheral sensors (a muscle stretch receptor in this case) initiates receptor potentials that trigger action potentials that travel centrally along the *afferent* axons of the sensory neurons. This information stimulates spinal motor neurons by means of synaptic contacts. The action potentials triggered by the synaptic potential in motor neurons travel peripherally in *efferent* axons, giving rise to muscle contraction and a behavioral response. One of the purposes of this particular reflex is to help maintain an upright posture in the face of unexpected changes.

carry information *toward* the brain or spinal cord (or farther centrally within the spinal cord and brain) are called **afferent neurons**; nerve cells that carry information *away* from the brain or spinal cord (or away from the circuit in question) are called **efferent neurons**. **Interneurons** or **local circuit neurons** only participate in the local aspects of a circuit, based on the short distances over which their axons extend. These three functional classes—afferent neurons, efferent neurons, and interneurons—are the basic constituents of all neural circuits.

A simple example of a neural circuit is the ensemble of cells that subserves the **myotatic spinal reflex** (the “knee-jerk” reflex; Figure 1.7). The afferent neurons of the reflex are **sensory neurons** whose cell bodies lie the **dorsal root ganglia** and whose peripheral axons terminate in sensory endings in skeletal muscles (the ganglia that serve this same of function for much of the head and neck are called **cranial nerve ganglia;** see Appendix A). The central axons of these afferent sensory neurons enter the the spinal cord where they terminate on a variety of central neurons concerned with the regualtion of muscle tone, most obviously the **motor neurons** that determine the activity of the related muscles. These neurons constitute the efferent neurons as well as interneurons of the circuit. One group of these efferent neurons in the ventral horn of the spinal cord projects to the flexor muscles in the limb, and the other to extensor muscles. Spinal cord interneurons are the third element of this circuit. The interneurons receive synaptic contacts from sensory afferent neurons and make synapses on the efferent motor neurons that project to the

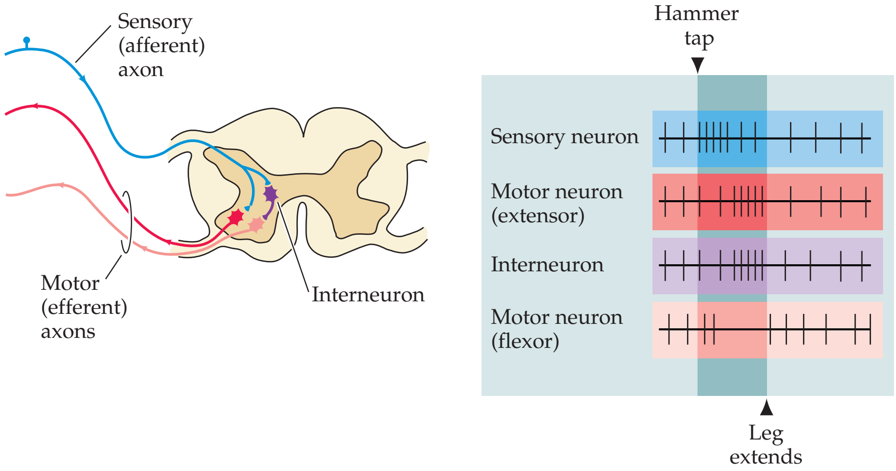


Figure 1.8 Relative frequency of action potentials (indicated by individual vertical lines) in different components of the myotatic reflex as the reflex pathway is activated. Notice the modulatory effect of the interneuron.

flexor muscles; therefore they are capable of modulating the input–output linkage. The excitatory synaptic connections between the sensory afferents and the extensor efferent motor neurons cause the extensor muscles to contract; at the same time, the interneurons activated by the afferents are inhibitory, and their activation diminishes electrical activity in flexor efferent motor neurons and causes the flexor muscles to become less active (Figure 1.8). The result is a complementary activation and inactivation of the synergist and antagonist muscles that control the position of the leg.

A more detailed picture of the events underlying the myotatic or any other circuit can be obtained by electrophysiological recording (Figure 1.9). There are two basic approaches to measuring the electrical activity of a nerve cell: **extracellular recording** (also referred to as single-unit recording), where an electrode is placed *near* the nerve cell of interest to detect its activity; and **intracellular recording**, where the electrode is placed *inside* the cell. Extracellular recordings primarily detect **action potentials**, the all-or-nothing changes in the potential across nerve cell membranes that convey information from one point to another in the nervous system. This sort of recording is particularly useful for detecting temporal patterns of action potential activity and relating those patterns to stimulation by other inputs, or to specific behavioral events. Intracellular recordings can detect the smaller, graded potential changes that trigger action potentials, and thus allow a more detailed analysis of communication between neurons within a circuit. These graded triggering potentials can arise at either sensory receptors or synapses and are called **receptor potentials** or **synaptic potentials**, respectively.

For the myotatic circuit, electrical activity can be measured both extracellularly and intracellularly, thus defining the functional relationships between neurons in the circuit. The pattern of action potential activity can be measured for each element of the circuit (afferents, efferents, and interneurons) before, during, and after a stimulus (see Figure 1.8). By comparing the onset, duration, and frequency of action potential activity in each cell, a functional picture of the circuit emerges. As a result of the stimulus, the sensory neuron is triggered to fire at higher frequency (i.e., more action potentials per unit time). This increase triggers a higher frequency of action potentials in both the extensor motor neurons and the interneurons. Concurrently, the inhibitory synapses made by the interneurons onto the flexor motor neurons cause the frequency of action potentials in these cells to decline. Using intracellular recording, it is possible to observe directly the potential changes underlying the synaptic connections of the myotatic reflex circuit (see Figure 1.9).

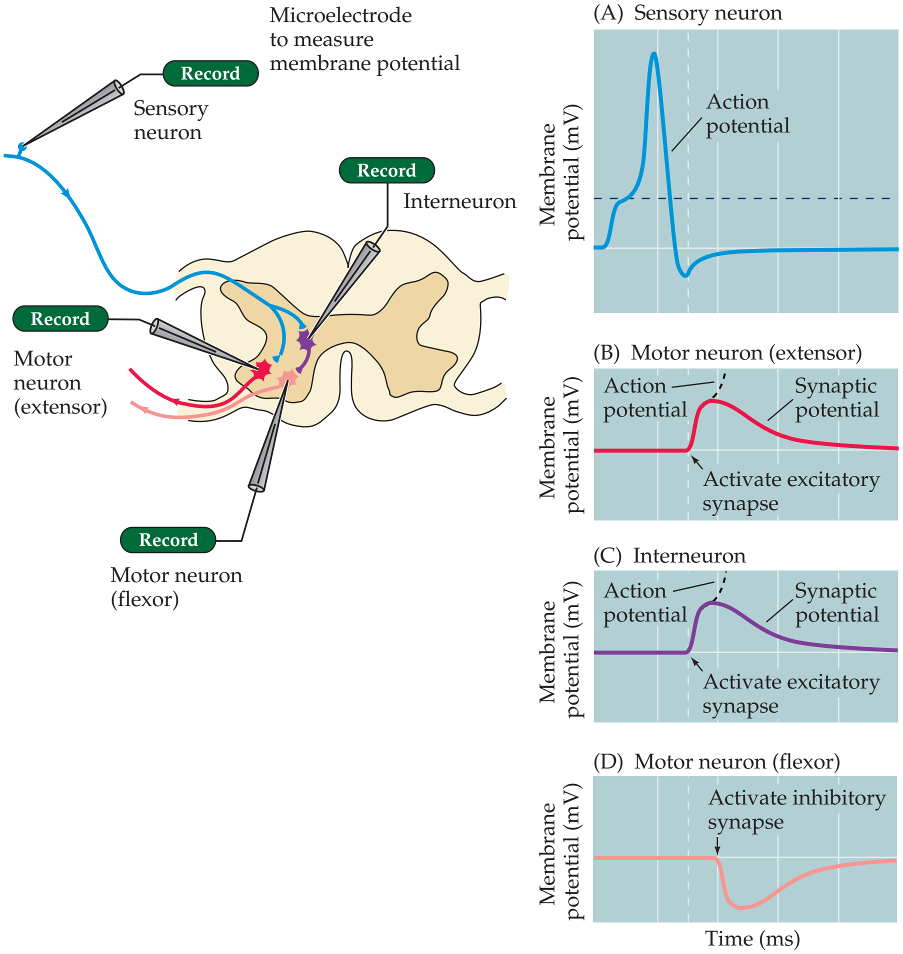

Microelectrode
to measure
membrane potential
Record
Sensory
neuron
Record
Interneuron
Record
Motor
neuron
(extensor)
Record
Motor neuron
(flexor)
(A) Sensory neuron
Membrane
potential (mV)
Action
potential
(B) Motor neuron (extensor)
Action
potential
Synaptic
potential
Activate excitatory
synapse
(C) Interneuron
Action
potential
Synaptic
potential
Activate excitatory
synapse
(D) Motor neuron (flexor)
Activate inhibitory
synapse
Time (ms)

Figure 1.9 Intracellularly recorded responses underlying the myotatic reflex. (A) Action potential measured in a sensory neuron. (B) Postsynaptic triggering potential recorded in an extensor motor neuron. (C) Postsynaptic triggering potential in an interneuron. (D) Postsynaptic inhibitory potential in a flexor motor neuron. Such intracellular recordings are the basis for understanding the cellular mechanisms of action potential generation, and the sensory receptor and synaptic potentials that trigger these conducted signals.

Overall Organization of the Human Nervous System

When considered together, circuits that process similar types of information comprise **neural systems** that serve broader behavioral purposes. The most general functional distinction divides such collections into **sensory systems** that acquire and process information from the environment (e.g., the visual system or the auditory system, see Unit II), and **motor systems** that respond to such information by generating movements and other behavior (see Unit III). There are, however, large numbers of cells and circuits that lie between these relatively well-defined input and output systems. These are collectively referred to as **associational systems**, and they mediate the most complex and least well-characterized brain functions (see Unit V).

In addition to these broad functional distinctions, neuroscientists and neurologists have conventionally divided the vertebrate nervous system anatomically into central and peripheral components (Figure 1.10). The **central nervous system**, typically referred to as the **CNS**, comprises the **brain** (cerebral hemispheres, diencephalon, cerebellum, and brainstem) and the **spinal cord** (see Appendix A for more information about the gross anatomical features of the CNS). The **peripheral nervous system** (**PNS**) includes the sensory neurons that link sensory receptors on the body surface or deeper within it with relevant processing circuits in the central nervous system. The motor portion of the peripheral nervous system in turn consists of two components. The motor axons that connect the brain and spinal cord to skeletal

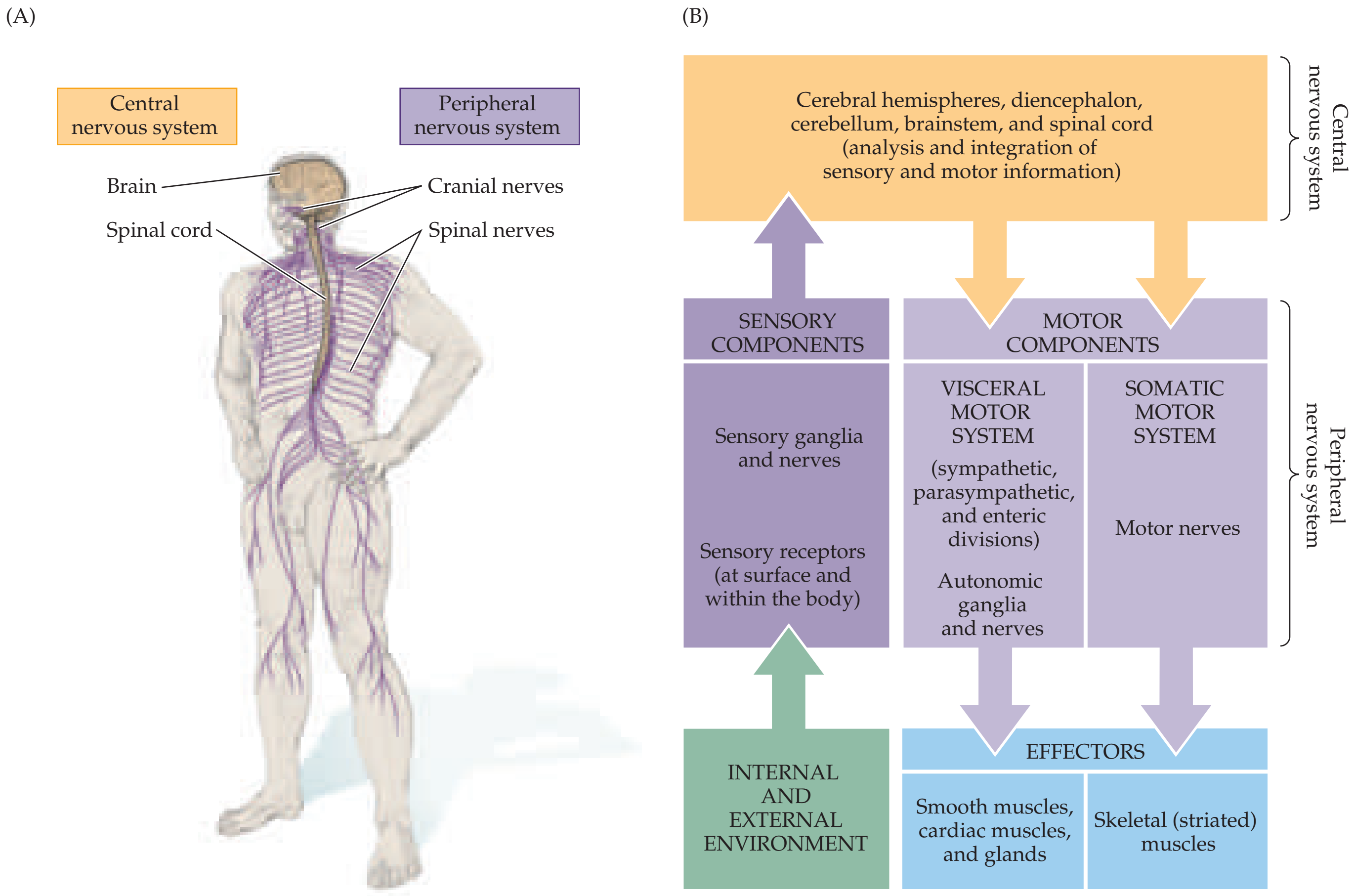

(A)
Central nervous system
Peripheral nervous system
Brain
Cranial nerves
Spinal cord
Spinal nerves
(B)
Cerebral hemispheres, diencephalon, cerebellum, brainstem, and spinal cord (analysis and integration of sensory and motor information)
Central nervous system
SENSORY COMPONENTS
MOTOR COMPONENTS
Sensory ganglia and nerves
Sensory receptors (at surface and within the body)
VISCERAL MOTOR SYSTEM
(sympathetic, parasympathetic, and enteric divisions)
Autonomic ganglia and nerves
SOMATIC MOTOR SYSTEM
Motor nerves
Peripheral nervous system
INTERNAL AND EXTERNAL ENVIRONMENT
EFFECTORS
Smooth muscles, cardiac muscles, and glands
Skeletal (striated) muscles

Figure 1.10 The major components of the nervous system and their functional relationships. (A) The CNS (brain and spinal cord) and PNS (spinal and cranial nerves). (B) Diagram of the major components of the central and peripheral nervous systems and their functional relationships. Stimuli from the environment convey information to processing circuits within the brain and spinal cord, which in turn interpret their significance and send signals to peripheral effectors that move the body and adjust the workings of its internal organs.

muscles make up the **somatic motor division** of the peripheral nervous system, whereas the cells and axons that innervate smooth muscles, cardiac muscle, and glands make up the **visceral** or **autonomic motor division**.

Those nerve cell bodies that reside in the peripheral nervous system are located in **ganglia**, which are simply local accumulations of nerve cell bodies (and supporting cells). Peripheral axons are gathered into bundles called **nerves**, many of which are enveloped by the glial cells of the peripheral nervous system called **Schwann cells**. In the central nervous system, nerve cells are arranged in two different ways. **Nuclei** are local accumulations of neurons having roughly similar connections and functions; such collections are found throughout the cerebrum, brainstem and spinal cord. In contrast, **cortex** (plural, *cortices*) describes sheet-like arrays of nerve cells (again, consult Appendix A for additional information and illustrations). The cortices of the cerebral hemispheres and of the cerebellum provide the clearest example of this organizational principle.

Axons in the central nervous system are gathered into **tracts** that are more or less analogous to nerves in the periphery. Tracts that cross the midline of the brain are referred to as **commissures**. Two gross histological terms distinguish regions rich in neuronal cell bodies versus regions rich in axons. **Gray matter** refers to any accumulation of cell bodies and neuropil in the brain and spinal cord (e.g., nuclei or cortices), whereas **white matter**, named for its relatively light appearance resulting from the lipid content of myelin, refers to axon tracts and commissures.

The organization of the visceral motor division of the peripheral nervous system is a bit more complicated (see Chapter 20). Visceral motor neurons in the brainstem and spinal cord, the so-called preganglionic neurons, form synapses with peripheral motor neurons that lie in the **autonomic ganglia**. The motor neurons in autonomic ganglia innervate smooth muscle, glands, and cardiac muscle, thus controlling most involuntary (visceral) behavior. In the **sympathetic division** of the autonomic motor system, the ganglia lie along or in front of the vertebral column and send their axons to a variety of peripheral targets. In the **parasympathetic division**, the ganglia are found within the organs they innervate. Another component of the visceral motor system, called the **enteric system**, is made up of small ganglia as well as individual neurons scattered throughout the wall of the gut. These neurons influence gastric motility and secretion.

Neuroanatomical Terminology

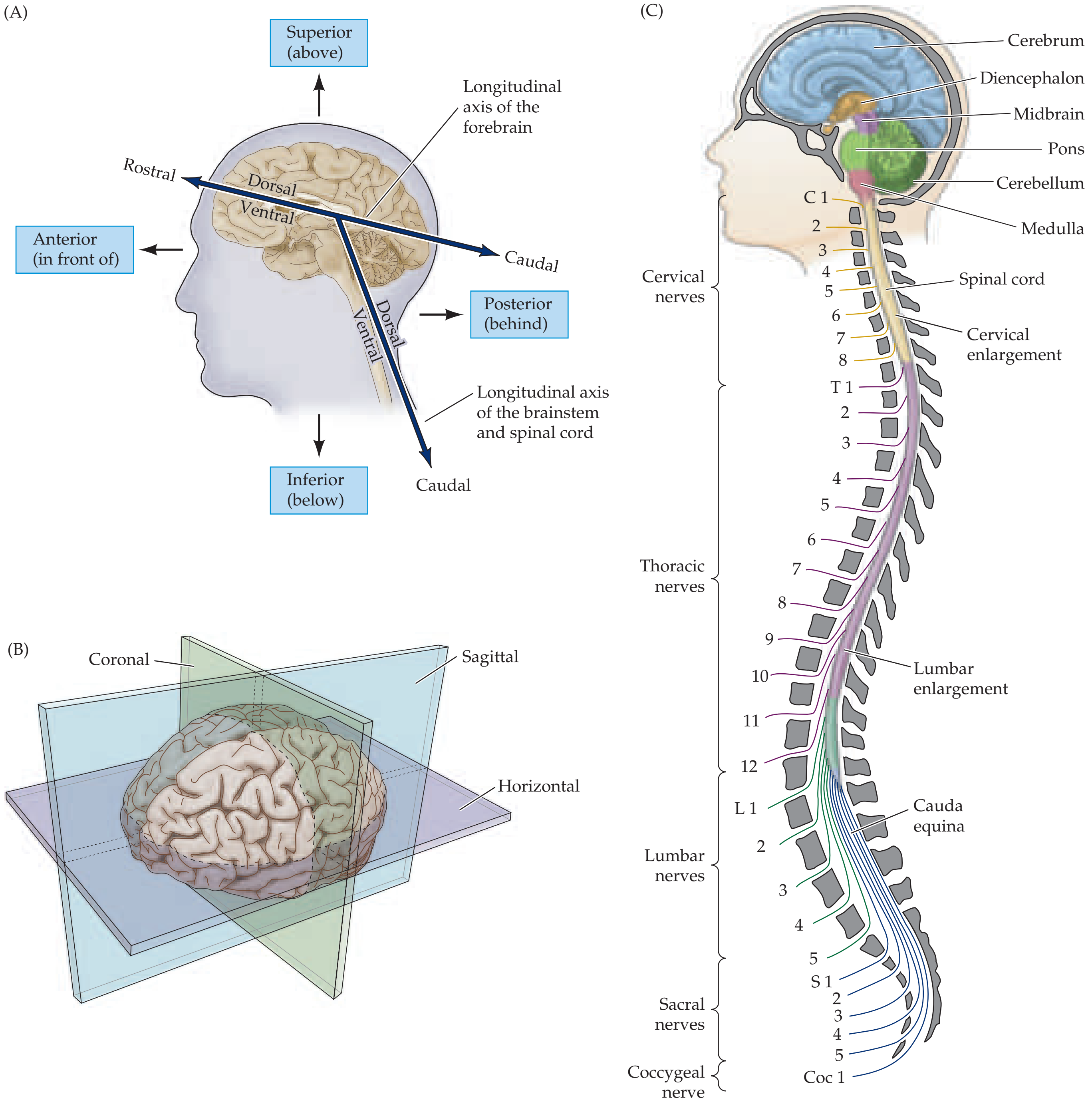
Describing the organization of any neural system requires a rudimentary understanding of anatomical terminology. The terms used to specify location in the central nervous system are the same as those used for the gross anatomical description of the rest of the body (Figure 1.11). Thus, *anterior* and *posterior* indicate front and back (head and tail); *rostral* and *caudal*, toward the head and tail; *dorsal* and *ventral*, top and bottom (back and belly); and *medial* and *lateral*, at the midline or to the side. Nevertheless, the comparison between these coordinates in the body versus the brain can be confusing. For the entire body these anatomical terms refer to the long axis, which is straight. The long axis of the central nervous system, however, has a bend in it. In humans and other bipeds, a compensatory tilting of the rostral–caudal axis for the brain is necessary to properly compare body axes to brain axes. Once this adjustment has been made, the other axes for the brain can be easily assigned.

The proper assignment of the anatomical axes then dictates the standard planes for histological sections or live images (see Box A) used to study the internal anatomy of the brain (see Figure 1.11B). **Horizontal sections** (also referred to as **axial** or **transverse** sections) are taken parallel to the rostral–caudal axis of the brain; thus, in an individual standing upright, such sections are parallel to the ground. Sections taken in the plane dividing the two hemispheres are **sagittal**, and can be further categorized as **midsagittal** and **parasagittal**, according to whether the section is near the midline (midsagittal)

Figure 1.11 A flexure in the long axis of the nervous system arose as humans evolved upright posture, leading to an approximately 120° angle between the long axis of the brainstem and that of the forebrain The consequences of this flexure for anatomical terminology are indicated in (A). The terms *anterior, posterior*, *superior*, and *inferior* refer to the long axis of the body, which is straight. Therefore, these terms indicate the same direction for both the forebrain and the brainstem. In contrast, the terms *dorsal*, *ventral*, *rostral*, and *caudal* refer to the long axis of the central nervous system. The dorsal direction is toward the back for the brainstem and spinal cord, but toward the top of the head for the forebrain. The opposite direction is ventral. The rostral direction is toward the top of the head for the brainstem and spinal cord, but toward the face for the forebrain. The opposite direction is caudal. (B) The major planes of section used in cutting or imaging the brain. (C) The subdivisions and components of the central nervous system. (Note that the position of the brackets on the left side of the figure refers to the vertebrae, not the spinal segments.)

▶

or more lateral (parasagittal). Sections in the plane of the face are called **coronal** or **frontal**. Different terms are usually used to refer to sections of the spinal cord. The plane of section orthogonal to the long axis of the cord is called **transverse**, whereas sections parallel to the long axis of the cord are called **longitudinal**. In a transverse section through the human spinal cord, the dorsal and ventral axes and the anterior and posterior axes indicate the same directions (see Figure 1.11). Tedious though this terminology may be, it


(A)
Superior (above)
Longitudinal axis of the forebrain
Rostral
Dorsal
Ventral
Caudal
Anterior (in front of)
Posterior (behind)
Dorsal
Ventral
Longitudinal axis of the brainstem and spinal cord
Inferior (below)
Caudal
(B)
Coronal
Sagittal
Horizontal
(C)
Cerebrum
Diencephalon
Midbrain
Pons
Cerebellum
Medulla
C 1
2
3
4
5
6
7
8
Cervical nerves
Spinal cord
Cervical enlargement
T 1
2
3
4
5
6
7
8
9
10
11
12
Thoracic nerves
Lumbar enlargement
L 1
2
3
4
5
Lumbar nerves
Cauda equina
S 1
2
3
4
5
Sacral nerves
Coc 1
Coccygeal nerve

is essential for understanding the basic subdivisions of the nervous system (Figure 1.11C).

The Subdivisions of the Central Nervous System

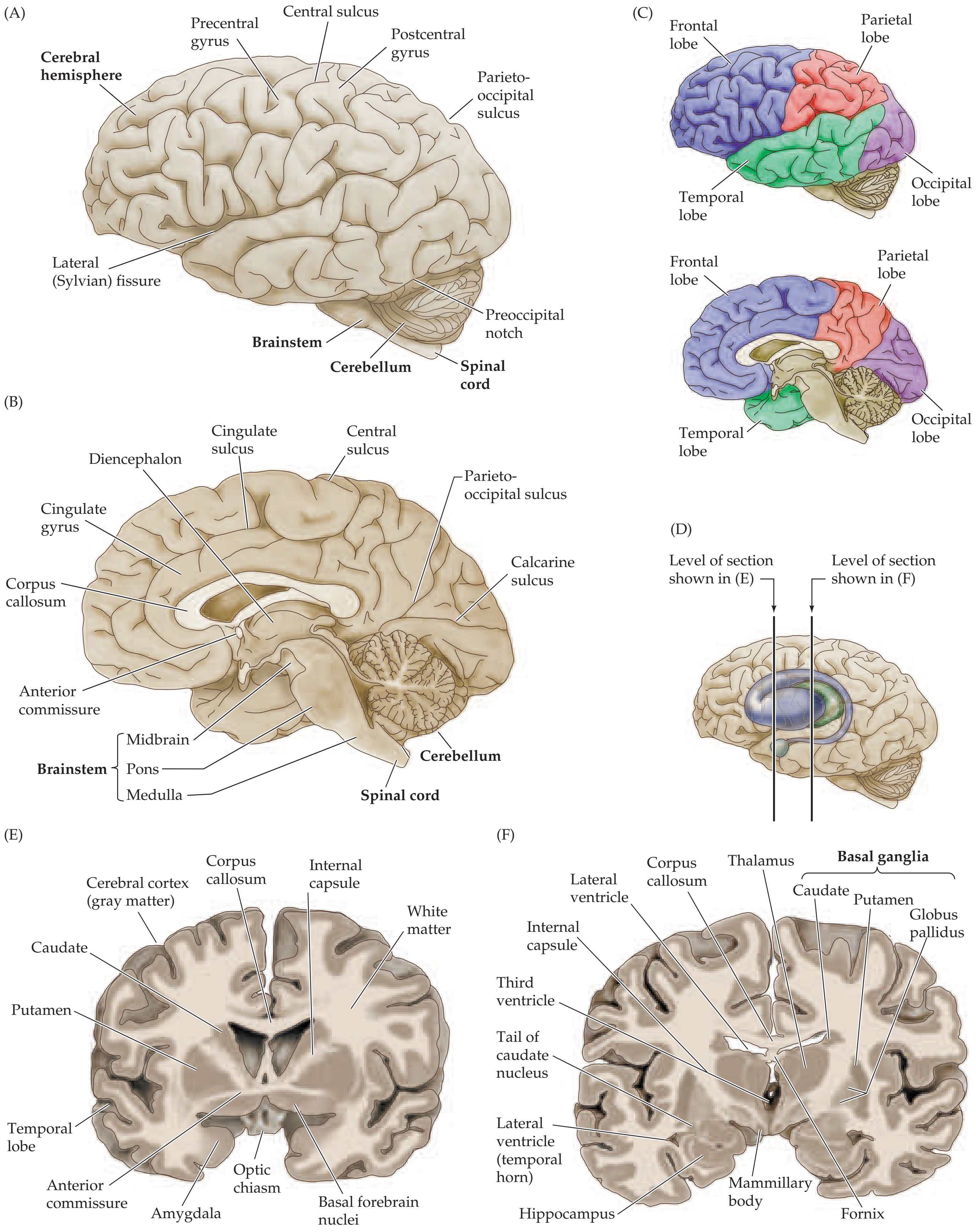
The central nervous system (defined as the brain and spinal cord) is usually considered to have seven basic parts: the **spinal cord**, the **medulla**, the **pons**, the **cerebellum**, the **midbrain**, the **diencephalon**, and the **cerebral hemispheres** (see Figures 1.10 and 1.11C). Running through all of these subdivisons are fluid-filled spaces called **ventricles** (a detailed account of the ventricular system can be found in Appendix B). These ventricles are the remnants of the continuous lumen initially enclosed by the neural plate as it rounded to become the neural tube during early development (see Chapter 21). Variations in the shape and size of the mature ventricular space are characteristic of each adult brain region. The medulla, pons, and midbrain are collectively called the **brainstem** and they surround the **4th ventricle** (medulla and pons) and **cerebral aqueduct** (midbrain). The diencephalon and cerebral hemispheres are collectively called the **forebrain,** and they enclose the **3rd and lateral ventricles**, respectively. Within the brainstem are the **cranial nerve nuclei** that either receive input from the **cranial sensory ganglia** mentioned earlier via the **cranial sensory nerves**, or give rise to axons that constitute the **cranial motor nerves** (see Appendix A).

The brainstem is also a conduit for several major tracts in the central nervous system that relay sensory information from the spinal cord and brainstem to the forebrain, or relay motor commands from forebrain back to motor neurons in the brainstem and spinal cord. Accordingly, detailed knowledge of the consequences of damage to the brainstem provides neurologists and other clinicians an essential tool in the localization and diagnosis of brain injury. The brainstem contains numerous additional nuclei that are involved in a myriad of important functions including the control of heart rate, respiration, blood pressure, and level of consciousness. Finally, one of the most prominent features of the brainstem is the **cerebellum,** which extends over much of its dorsal aspect. The cerebellum is essential for the coordination and planning of movements (see Chapter 18) as well as learning motor tasks and storing that information (see Chapter 30).

There are several anatomical subdivisions of the forebrain. The most obvious anatomical structures are the prominent **cerebral hemispheres** (Figure 1.12). In humans, the cerebral hemispheres (the outermost portions of which are continuous, highly folded sheets of cortex) are proportionally larger than in any other mammal, and are characterized by the **gyri** (singular, *gyrus*) or crests of folded cortical tissue, and **sulci** (singular, *sulcus*) the grooves that divide gyri from one another (as pictured on the cover of this book, for example). Although gyral and sulcal patterns vary from individual to individual, there are some fairly consistent landmarks that help divide the hemispheres into four **lobes**. The names of the lobes are derived from the cranial bones that overlie them: **occipital**, **temporal**, **parietal**, and **frontal**. A key feature of the surface anatomy of the cerebrum is the **central sulcus** located

sylvius

Figure 1.12 Gross anatomy of the forebrain (A) Cerebral hemisphere surface anatomy, showing the four lobes of the brain and the major sulci and gyri. The ventricular system and basal ganglia can also be seen in this phantom view. (B) Midsagittal view showing the location of the hippocampus, amygdala, thalamus and hypothalamus.


(A)
Cerebral hemisphere
Precentral gyrus
Central sulcus
Postcentral gyrus
Parieto-occipital sulcus
Lateral (Sylvian) fissure
Preoccipital notch
Brainstem
Cerebellum
Spinal cord
(B)
Diencephalon
Cingulate sulcus
Central sulcus
Parieto-occipital sulcus
Cingulate gyrus
Corpus callosum
Calcarine sulcus
Anterior commissure
Brainstem
Midbrain
Pons
Medulla
Cerebellum
Spinal cord
(C)
Frontal lobe
Parietal lobe
Temporal lobe
Occipital lobe
Frontal lobe
Parietal lobe
Temporal lobe
Occipital lobe
(D)
Level of section shown in (E)
Level of section shown in (F)
(E)
Cerebral cortex (gray matter)
Corpus callosum
Internal capsule
White matter
Caudate
Putamen
Temporal lobe
Anterior commissure
Amygdala
Optic chiasm
Basal forebrain nuclei
(F)
Lateral ventricle
Corpus callosum
Thalamus
Basal ganglia
Caudate
Putamen
Globus pallidus
Internal capsule
Third ventricle
Tail of caudate nucleus
Lateral ventricle (temporal horn)
Hippocampus
Mammillary body
Fornix

roughly halfway between the rostral and caudal poles of the hemispheres (Figure 1.12A). This prominent sulcus divides the frontal lobe at the rostral end of the hemisphere from the more caudal parietal lobe. Prominent on either side of the central sulcus are the pre- and postcentral gyri. These gyri are also functionally significant in that the precentral gyrus contains the primary motor cortex important for the control of movement, and the postcentral gyrus contains the primary somatic sensory cortex which is important for the bodily senses (see below).

The remaining subdivisions of the forebrain lie deeper in the cerebral hemispheres (Figure 1.12B). The most prominent of these is the collection of deep structures involved in motor and cognitive processes collectively referred to as the **basal ganglia.** Other particularly important structures are the **hippocampus** and **amygdala** in the temporal lobes (these are vital substrates for memory and emotional behavior, respectively), and the **olfactory bulbs** (the central stations for processing chemosensory information arising from receptor neurons in the nasal cavity) on the anterior–inferior aspect of the frontal lobes. Finally, the **thalamus** lies in the diencephalon and is a critical relay for sensory information (although it has many other functions as well); the **hypothalamus**, which as the name implies lies below the thalamus, is the central organizing structure for the regulation of the body’s many homeostatic functions (e.g., feeding, drinking, thermoregulation).

This rudimentary description of some prominent anatomical landmarks provides a framework for understanding how neurons resident in a number of widely distributed and distinct brain structures communicate with one another to define **neural systems** dedicated to encoding, processing and relaying specific sorts of information about aspects of the organism’s environment, and then initiating and coordinating appropriate behavioral responses.

Organizational Principles of Neural Systems

These complex perceptual and motor capacities of the brain reflect the integrated function of various neural systems. The processing of somatic sensory information (arising from receptors in the skin, subcutaneous tissues, and the musculoskeletal system that respond to physical deformation at the body surface or displacement of muscles and joints) provides a convenient example. These widely distributed structures that participate in generating somatic sensations are referred to as the **somatic sensory system** (Figure 1.13). The components in the peripheral nervous system include the receptors distributed throughout the skin as well as in muscles and tendons, the related neurons in dorsal root ganglia, and neurons in some cranial ganglia. The central nervous system components include neurons in the spinal cord, as well as the long tracts of their axons that originate in the spinal cord, travel through the brainstem, and ultimately terminate in distinct **relay nuclei** in the thalamus in the diencephalon. The still-higher targets of the thalamic neurons are the cortical areas around the postcentral gyrus that are collectively referred to as the **somatic sensory cortex**. Thus, the somatic sensory system includes specific populations of neurons in practically every subdivision of the nervous system.

Two further principles of neural system organization are evident in the somatic sensory system: **topographic organization** and the prevalence of **parallel pathways** (see Figure 1.13). As the name implies, topography refers to a mapping function—in this case a map of the body surface that can be discerned within the various structures that constitute the somatic sensory

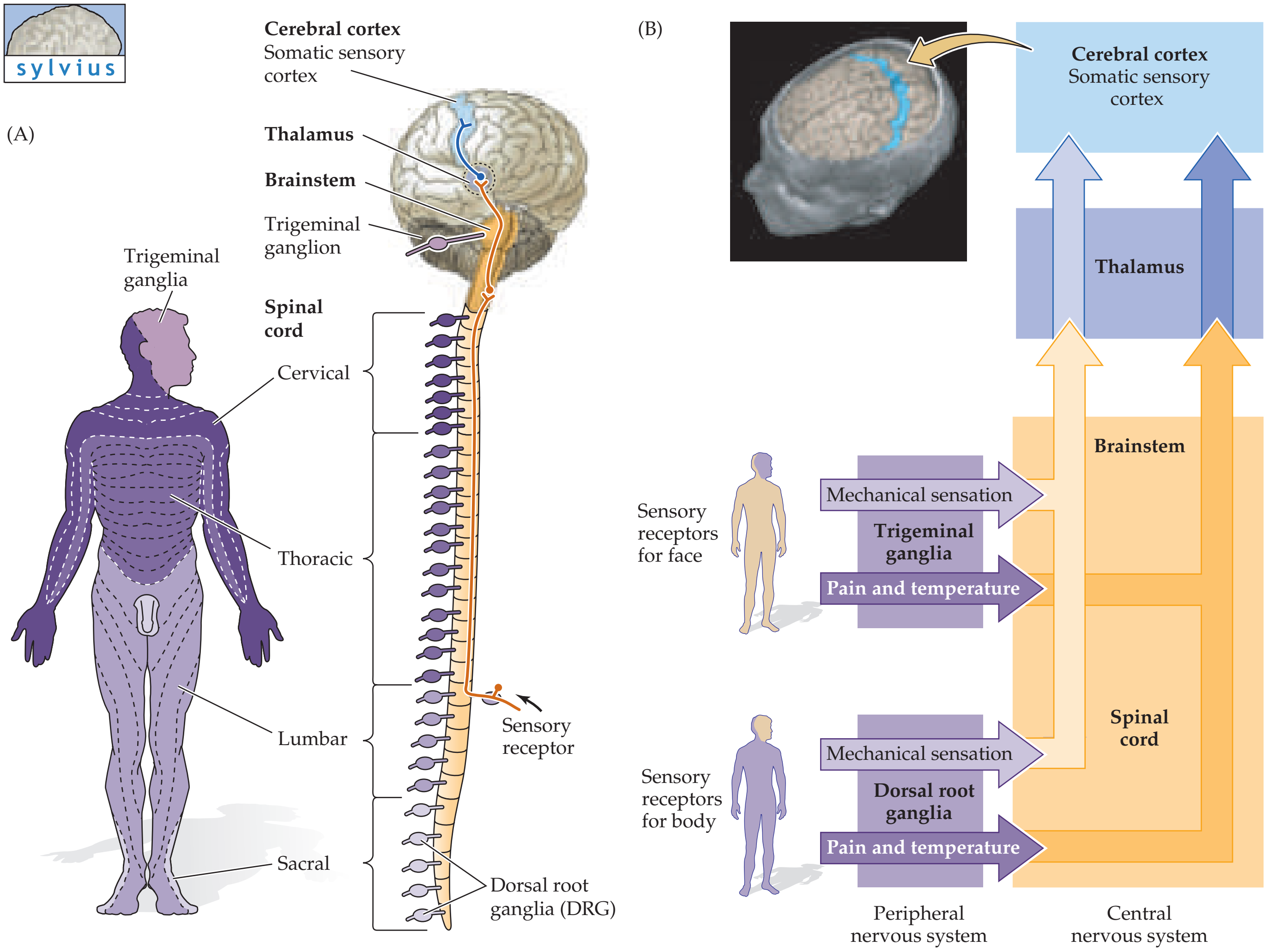

sylvius
(A)
Cerebral cortex
Somatic sensory cortex
Thalamus
Brainstem
Trigeminal ganglion
Trigeminal ganglia
Spinal cord
Cervical
Thoracic
Lumbar
Sacral
Sensory receptor
Dorsal root ganglia (DRG)
(B)
Cerebral cortex
Somatic sensory cortex
Thalamus
Brainstem
Spinal cord
Sensory receptors for face
Mechanical sensation
Trigeminal ganglia
Pain and temperature
Sensory receptors for body
Mechanical sensation
Dorsal root ganglia
Pain and temperature
Peripheral nervous system
Central nervous system

Figure 1.13 The anatomical and functional organization of the somatic sensory system. Central nervous system components of the somatic sensory system are found in the spinal cord, brainstem, thalamus, and cerebral cortex. (A) Somatosensory information from the body surface is mapped onto dorsal root ganglia (DRG), schematically depicted here as attachments to the spinal cord. The various shades of purple indicate correspondence between regions of the body and the DRG that relay information from the body surface to the central nervous system. Information from the head and neck is relayed to the CNS via the trigeminal ganglia. (B) Somatosensory information travels from the peripheral sensory receptors via parallel pathways for mechanical sensation and for the sensation of pain and temperature. These parallel pathways relay through the spinal cord and brainstem, ultimately sending sensory information to the thalamus, from which it is relayed to the somatic sensory cortex in the postcentral gyrus (indicated in blue in the image of the whole brain; MRI courtesy of L. E. White, J. Vovoydic, and S. M. Williams).

system. Thus, adjacent areas on the body surface are mapped to adjacent regions in nuclei, in white matter tracts, and in the thalamic and cortical targets of the system. Beginning in the periphery, the cells in each dorsal root ganglion define a discrete **dermatome** (the area of the skin innervated by the processes of cells from a single dorsal root). In the spinal cord, from caudal to rostral, the dermatomes are represented in corresponding regions of the spinal cord from sacral (back) to lumbar (legs) to thoracic (chest) and cervical (arms and shoulders) (see Figures 1.13 and 1.11C). This so-called **somatotopy** is maintained in the somatic sensory tracts in spinal cord and brainstem that convey information to the relevant forebrain structures of the somatic sensory system (Figure 1.14).

Parallel pathways refer to the segregation of nerve cell axons that process the distinct stimulus attributes that comprise a particular sensory, motor, or cognitive modality. For somatic sensation, the stimulus attributes relayed via parallel pathways are pain, temperature, touch, pressure, and proprioception (the sense of joint or limb position). From the dorsal root ganglia, through the spinal cord and brainstem, and on to the somatic sensory cortex, these submodalities are kept largely segregated. Thus anatomically, biochemically, and physiologically distinct neurons transduce, encode, and relay pain, temperature, and mechanical information. Although this information is subsequently integrated to provide unitary perception of the relevant stimuli, neurons and circuits in the somatic sensory system are clearly specialized to process discrete aspects of somatic sensation.

This basic outline of the organization of the somatic system is representative of the principles pertinent to understanding any neural system. It will in every case be pertinent to consider the anatomical distribution of neural circuits dedicated to a particular function, how the function is represented or "mapped" onto the neural elements within the system, and how distinct stimulus attributes are segregated within subsets of neurons that comprise the system. Such details provide a framework for understanding how activity within the system provides a representation of relevant stimulus, the required motor response, and higher order cognitive correlates.

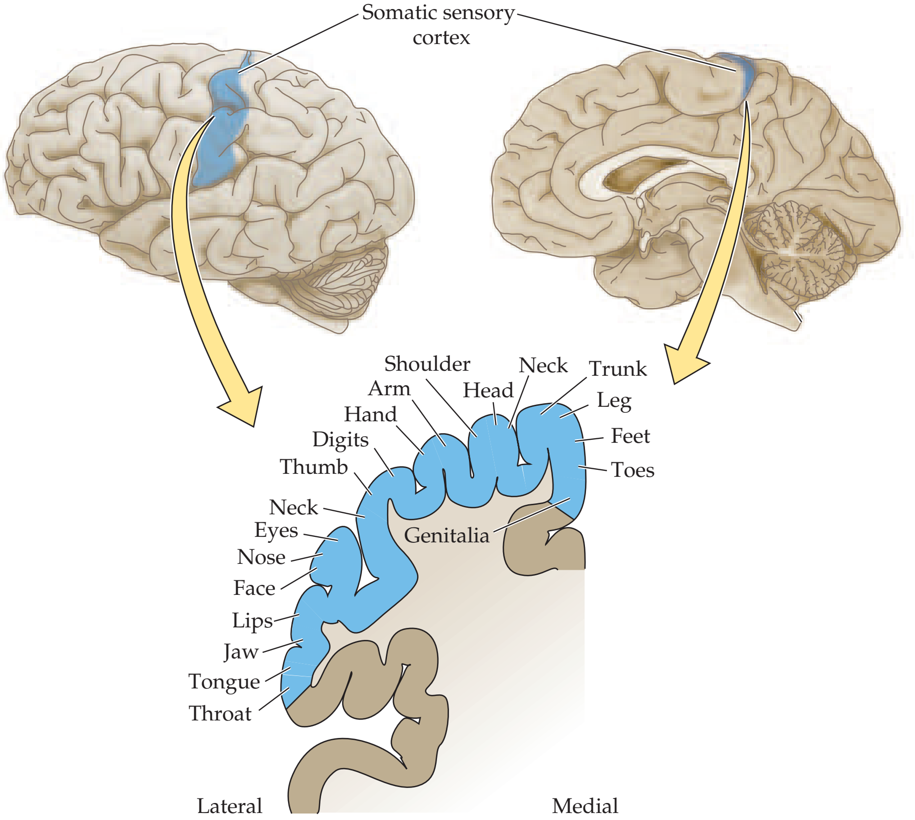


Figure 1.14 Somatotopic organization of sensory information. *(Top)* The locations of primary and secondary somatosensory cortical areas on the lateral surface of the brain. *(Bottom)* Cortical representation of different regions of skin.

Functional Analysis of Neural Systems

A wide range of physiological methods is now available to evaluate the electrical (and metabolic) activity of the neuronal circuits that make up a neural system. Two approaches, however, have been particularly useful in defining how neural systems represent information. The most widely used method is **single-cell**, or **single-unit electrophysiological recording** with microelectrodes (see above; this method often records from several nearby cells in addition to the one selected, providing further useful information). The use of microelectrodes to record action potential activity provides a cell-by-cell analysis of the organization topographic maps (Figure 1.15), and can give specific insight into the type of stimulus to which the neuron is "tuned" (i.e., the stimulus that elicits a maximal change in action potential activity from the baseline state). Single-unit analysis is often used to define a neuron's **receptive field**—the region in sensory space (e.g., the body surface, or a specialized structure such as the retina) within which a specific stimulus elicits the greatest action potential response. This approach to understanding neural systems was introduced by Stephen Kuffler and Vernon Mountcastle in the early 1950s and has now been used by several generations of neuroscientists to evaluate the relationship between stimuli and neuronal responses in both sensory and motor systems. Electrical recording techniques

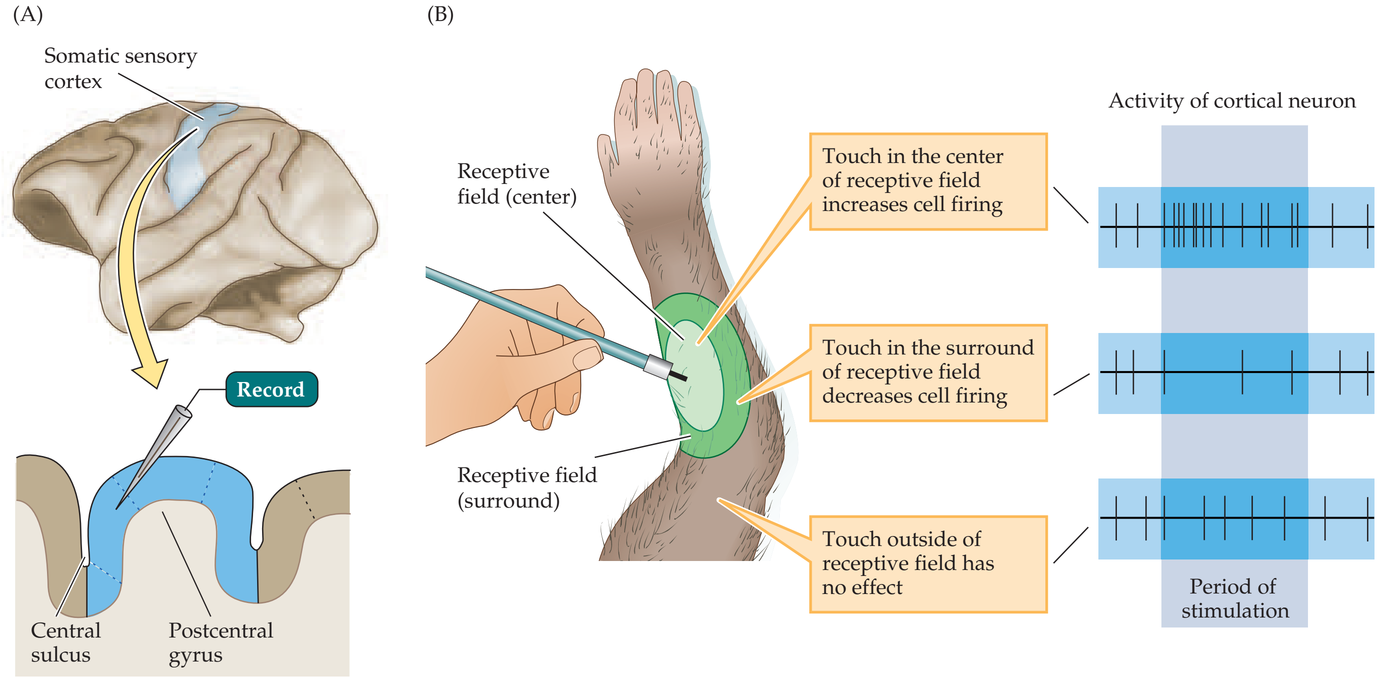

(A)
Somatic sensory cortex
Record
Central sulcus
Postcentral gyrus
(B)
Receptive field (center)
Receptive field (surround)
Touch in the center of receptive field increases cell firing
Touch in the surround of receptive field decreases cell firing
Touch outside of receptive field has no effect
Activity of cortical neuron
Period of stimulation

Figure 1.15 Single-unit electrophysiological recording from cortical pyramidal neuron, showing the firing pattern in response to a specific peripheral stimulus. (A) Typical experimental set-up. (B) Defining neuronal receptive fields.

at the single-cell level have now been extended and refined to include single and simultaneous multiple cell analysis in animals performing complex cognitive tasks, intracellular recordings in intact animals, and the use of patch electrodes to detect and monitor the activity of the individual membrane molecules that ultimately underlie neural signaling (see Unit I).

The second major area in which remarkable technical advances have been made is **functional brain imaging** in human subjects (and to a lesser extent animals), which has revolutionized the functional understanding of neural systems over the last two decades (Box A). Unlike electrical methods of recording neural activity, which are invasive in the sense of having to expose the brain and insert electrodes into it, functional imaging is noninvasive and thus applicable to both patients and normal human subjects. Moreover, functional imaging allows the simultaneous evaluation of multiple brain structures (which is possible but obviously difficult with electrical recording methods). The tasks that can be evaluated with functional imaging permit a far more ambitious and integrative approach to studying the operations of a neural system.

Over the last 20 years, these noninvasive methods have allowed neuroscientists to evaluate the representation of an enormous number of complex human behaviors, and at the same time have provided diagnostic tools that are used more and more routinely. Many of the resulting observations have confirmed inferences about functional localization and the organization of neural systems that were originally based on the study of neurological patients who exhibited altered behavior after stroke or other forms of brain injury. Others findings, however, have given new insights into the way neural systems function in the human brain.

Analyzing Complex Behavior

Many of the most widely heralded advances in modern neuroscience have involved reducing the complexity of the brain to more readily analyzed components—i.e., genes, molecules, or cells. Nevertheless, the brain functions as a whole, and the study of more complex (and, some might argue, more interesting) brain functions such as perception, language, emotion, memory, and consciousness remain a central challenge for contemporary neuroscientists. In recognition of this challenge, over the last 20 years or so a field called **cognitive neuroscience** has emerged that is specifically devoted to understanding these issues (see Unit V). This evolution has also rejuvenated the field of neuroethology (which is devoted to observing complex behaviors of animals in their native environments—for example, social communication in birds and non-human primates), and has encouraged the development of tasks to better evaluate the genesis of complex behaviors in human subjects. When used in combination with functional imaging, well designed behavioral tasks can facilitate identification of brain networks devoted to specific complex functions, including language skills, mathematical and musical ability, emotional responses, aesthetic judgments, and abstract thinking. Carefully constructed behavioral tasks can also be used to study the pathology of complex brain diseases that compromise cognition, such Alzheimer's disease, schizophrenia, and depression.

In short, new or revitalized efforts to study higher brain functions with increasingly powerful techniques offer ways of beginning to understand even the most complex aspects of human behavior.

Box A
Brain Imaging Techniques

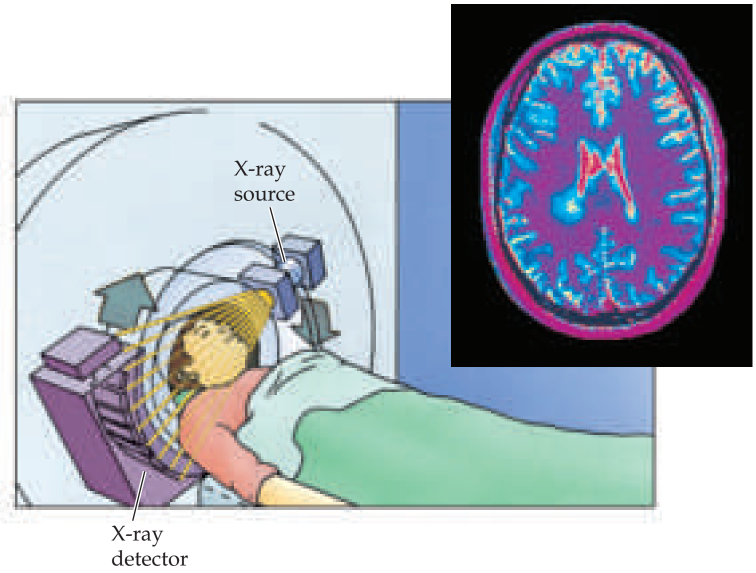
In the 1970s, **computerized tomography**, or **CT**, opened a new era in noninvasive imaging by introducing the use of computer processing technology to help probe the living brain. Prior to CT, the only brain imaging technique available was standard X-ray film, which has poor soft tissue contrast and involves relatively high radiation exposure.

The CT approach uses a narrow X-ray beam and a row of very sensitive detectors placed on opposite sides of the head to probe just a small portion of tissue at a time with limited radiation exposure (see Figure A). In order to make an image, the X-ray tube and detectors rotate around the head to collect radiodensity information from every orientation around a narrow slice. Computer processing techniques then calculate the radiodensity of each point within the slice plane, producing a tomographic image (*tomo* means "cut" or "slice"). If the patient is slowly moved through the scanner while the X-ray tube rotates in this way, a three-dimensional radiodensity matrix can be created, allowing images to be computed for any plane through the brain. CT scans can readily distinguish gray matter and white matter, differentiate the ventricles quite well, and show many other brain structures with a spatial resolution of several millimeters.

Brain imaging took another large step forward in the 1980s with the development of **magnetic resonance imaging** (**MRI**). MRI is based on the fact that the nuclei of some atoms act as spinning magnets, and that if they are placed in a strong magnetic field they will line up with the field and spin at a frequency that is dependent on the field strength. If they then receive a brief radiofrequency pulse tuned to their spinning frequency they are knocked out of alignment with the field, and subsequently emit energy in an oscillatory fashion as they gradually realign themselves with the field. The strength of the emitted signal depends on how many nuclei are involved in this process. To get spatial information in MRI, the magnetic field is distorted slightly by imposing magnetic gradients along three different spatial axes so that only nuclei at certain locations are tuned to the detector's frequency at any given time. Almost all MRI scanners use detectors tuned to the radio frequencies of spinning hydrogen nuclei in water molecules, and thus create images based on the distribution of water in different tissues. Careful manipulation of magnetic field gradients and radiofrequency pulses make it possible to construct extraordinarily detailed images of the brain at any location and orientation with sub-millimeter resolution.

The strong magnetic field and radiofrequency pulses used in MRI scanning are harmless, making this technique completely noninvasive (although metal objects in or near a scanner are a safety concern) (see Figure B). MRI is also extremely versatile because, by changing the scanning parameters, images based on a wide variety of different contrast mechanisms can be generated. For example, conventional MR images take advantage of the fact that hydrogen in different types of tissue (e.g., gray matter, white matter, cerebrospinal fluid) have slightly different realignment rates, meaning that soft tissue contrast can be manipulated simply by adjusting when the realigning hydrogen signal is measured. Different parameter settings can also be used to generate images in which gray and white matter are invisible but in which the brain vasculature stands out in sharp detail. Safety and versatility have made MRI the technique of choice for imaging brain structure in most applications.

Imaging functional variations in the living brain has also become possible with the recent development of techniques for detecting small, localized



(A) In computerized tomography, the X-ray source and detectors are moved around the patient's head. The inset shows a horizontal CT section of a normal adult brain.

(continued)

Box A (continued)

Brain Imaging Techniques

changes in metabolism or cerebral blood flow. To conserve energy, the brain regulates its blood flow such that active neurons with relatively high metabolic demands receive more blood than relatively inactive neurons. Detecting and mapping these local changes in cerebral blood flow forms the basis for three widely used functional brain imaging techniques: **positron emission tomography** (**PET**), **single-photon emission computerized tomography** (**SPECT**), and **functional magnetic resonance imaging** (**fMRI**).

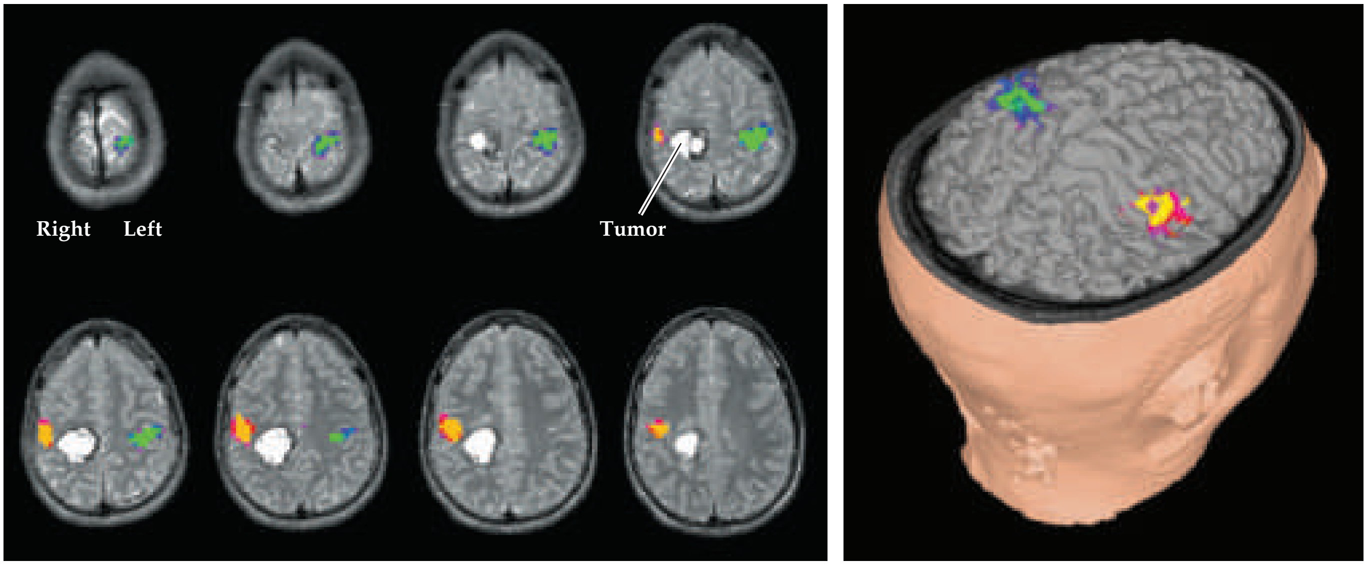
In PET scanning, unstable positron-emitting isotopes are incorporated into different reagents (including water, precursor molecules of specific neurotransmitters, or glucose) and injected into the bloodstream. Labeled oxygen and glucose quickly accumulate in more metabolically active areas, and labeled transmitter probes are taken up selectively by appropriate regions. As the unstable isotope decays, it results in the emission of two positrons moving in opposite directions. Gamma ray detectors placed around the head register a “hit” only when two detectors 180° apart react simultaneously. Images of tissue isotope density can then be generated (much the way CT images are calculated) showing the location of active regions with a spatial resolution of about 4 mm. Depending on the probe injected, PET imaging can be used to visualize activity-dependent changes in blood flow, tissue metabolism, or biochemical activity. SPECT imaging is similar to PET in that it involves injection or inhalation of a radiolabeled compound (for example, ^{133}Xe or ^{123}I-labeled iodoamphetamine), which produce photons that are detected by a gamma camera moving rapidly around the head.

Functional MRI, a variant of MRI, currently offers the best approach for visualizing brain function based on local metabolism. fMRI is predicated on the fact that hemoglobin in blood slightly distorts the magnetic resonance properties of hydrogen nuclei in its vicinity, and

(B) In MRI scanning, the head is placed in the center of a large magnet. A radiofrequency antenna coil is placed around the head for exciting and recording the magnetic resonance signal. For fMRI, stimuli can be presented using virtual reality video goggles and stereo headphones while inside the scanner.

Summary

The brain can be studied by methods that range from genetics and molecular biology to behavioral testing of normal human subjects. In addition to an ever-increasing store of knowledge about the anatomical organization of the nervous system, many of the brightest successes of modern neuroscience have come from understanding nerve cells as the basic structural and functional unit of the nervous system. Studies of the distinct cellular architecture and molecular components of neurons and glia have revealed much about



(C) MRI images of an adult patient with a brain tumor, with *f*MRI activity during a hand motion task superimposed (left hand activity is shown in yellow, right hand activity in green). At right is a three-dimensional surface reconstructed view of the same data.

the amount of magnetic distortion changes depending on whether the hemoglobin has oxygen bound to it. When a brain area is activated by a specific task it begins to use more oxygen and within seconds the brain microvasculature responds by increasing the flow of oxygen-rich blood to the active area. These changes in the concentration of oxygen and blood flow lead to localized blood oxygenation level-dependent (BOLD) changes in the magnetic resonance signal. Such fluctuations are detected using statistical image processing techniques to produce maps of task-dependent brain function (see Figure C). Because fMRI uses signals intrinsic to the brain without any radioactivity, repeated observations can be made on the same individual—a major advantage over imaging methods such as PET. The spatial resolution (2–3 mm) and temporal resolution (a few seconds) of fMRI are also superior to other functional imaging techniques. MRI has thus emerged as the technology of choice for probing both the structure and function of the living human brain.

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their individual functions, as well as providing a basis for understanding how nerve cells are organized into circuits, and circuits into systems that process specific types of information pertinent to perception and action. Goals that remain include understanding how basic molecular genetic phenomena are linked to cellular, circuit, and system functions; understanding how these processes go awry in neurological and psychiatric diseases; and beginning to understand the especially complex functions of the brain that make us human.

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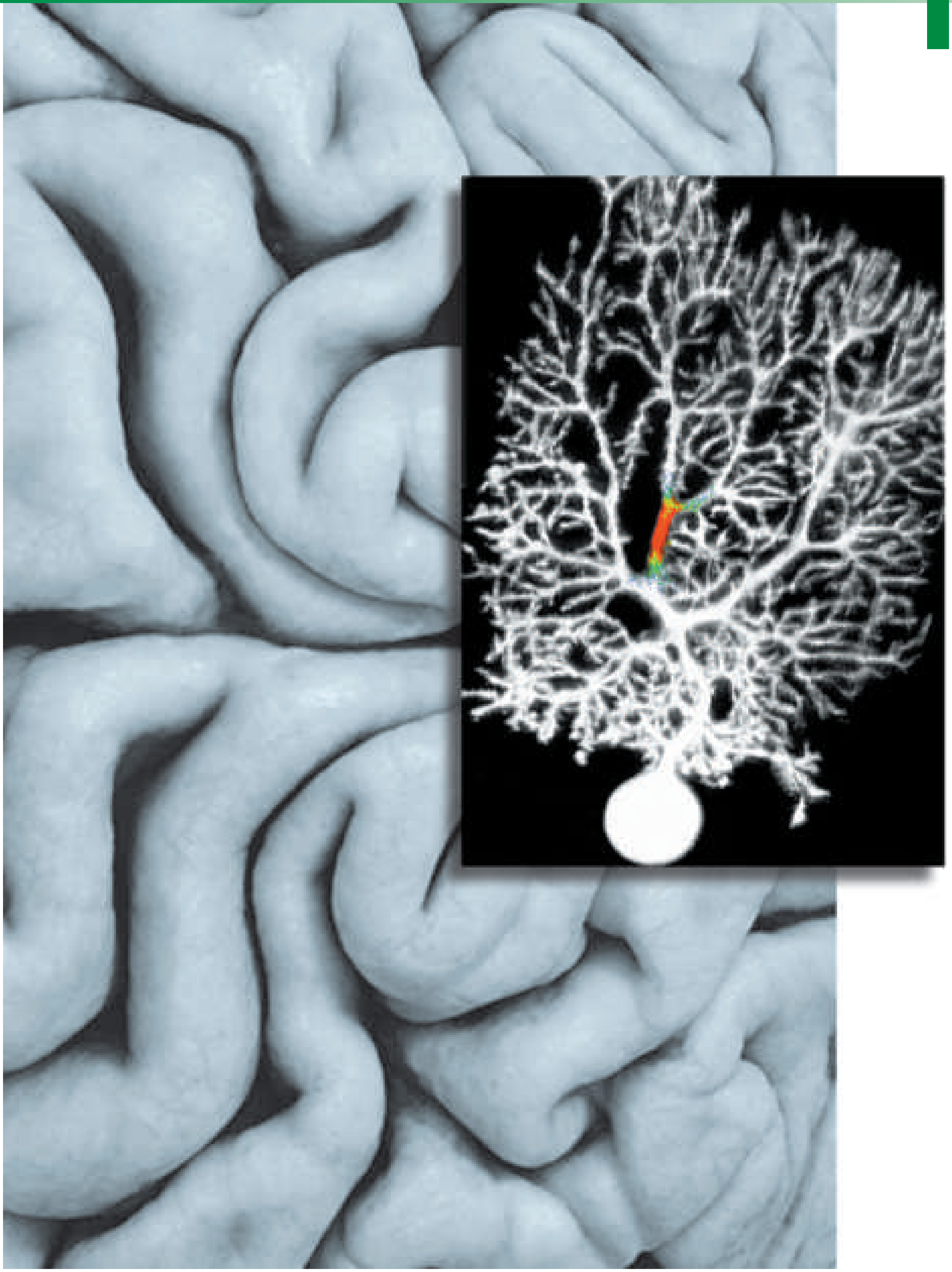
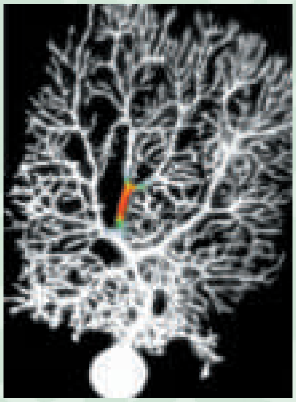
Neural Signaling





Calcium signaling in a cerebellar Purkinje neuron. An electrode was used to fill the neuron with a fluorescent calcium indicator dye. This dye revealed the release of intracellular calcium ions (color) produced by the actions of the second messenger IP_3. (Courtesy of Elizabeth A. Finch and George J. Augustine.)

UNIT I

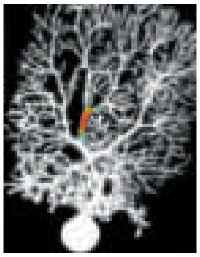
NEURAL SIGNALING

2 *Electrical Signals of Nerve Cells*
3 *Voltage-Dependent Membrane Permeability*
4 *Channels and Transporters*
5 *Synaptic Transmission*
6 *Neurotransmitters, Receptors, and Their Effects*
7 *Molecular Signaling within Neurons*

The brain is remarkably adept at acquiring, coordinating, and disseminating information about the body and its environment. Such information must be processed within milliseconds, yet it also can be stored away as memories that endure for years. Neurons within the central and peripheral nervous systems perform these functions by generating sophisticated electrical and chemical signals. This unit describes these signals and how they are produced. It explains how one type of electrical signal, the action potential, allows information to travel along the length of a nerve cell. It also explains how other types of signals—both electrical and chemical—are generated at synaptic connections between nerve cells. Synapses permit information transfer by interconnecting neurons to form the circuitry on which neural processing depends. Finally, it describes the intricate biochemical signaling events that take place within neurons. Appreciating these fundamental forms of neuronal signaling provides a foundation for appreciating the higher-level functions considered in the rest of the book.

The cellular and molecular mechanisms that give neurons their unique signaling abilities are also targets for disease processes that compromise the function of the nervous system. A working knowledge of the cellular and molecular biology of neurons is therefore fundamental to understanding a variety of brain pathologies, and for developing novel approaches to diagnosing and treating these all too prevalent problems.

Chapter 2



Electrical Signals of Nerve Cells

Overview

Nerve cells generate electrical signals that transmit information. Although neurons are not intrinsically good conductors of electricity, they have evolved elaborate mechanisms for generating these signals based on the flow of ions across their plasma membranes. Ordinarily, neurons generate a negative potential, called the resting membrane potential, that can be measured by recording the voltage between the inside and outside of nerve cells. The action potential transiently abolishes the negative resting potential and makes the transmembrane potential positive. Action potentials are propagated along the length of axons and are the fundamental signal that carries information from one place to another in the nervous system. Still other types of electrical signals are produced by the activation of synaptic contacts between neurons or by the actions of external forms of energy on sensory neurons. All of these electrical signals arise from ion fluxes brought about by nerve cell membranes being selectively permeable to different ions, and from the non-uniform distribution of these ions across the membrane.

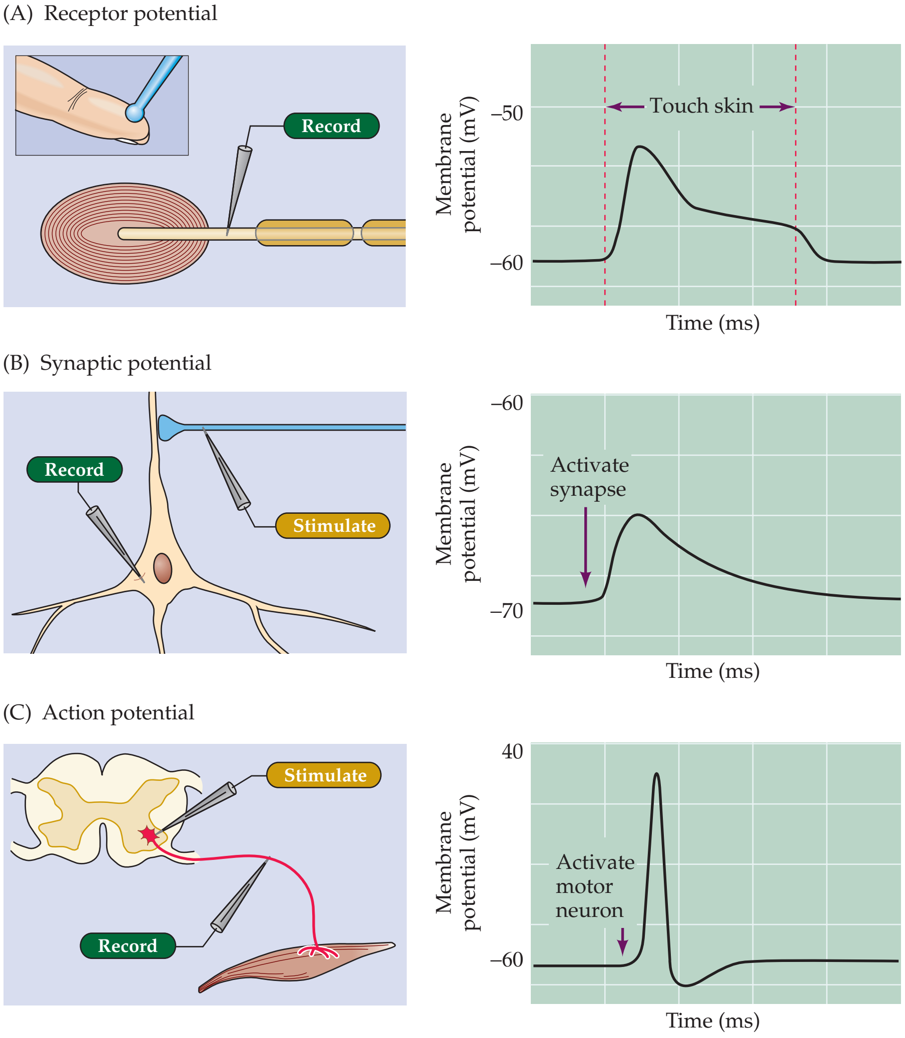
Electrical Potentials across Nerve Cell Membranes

Neurons employ several different types of electrical signal to encode and transfer information. The best way to observe these signals is to use an intracellular microelectrode to measure the electrical potential across the neuronal plasma membrane. A typical microelectrode is a piece of glass tubing pulled to a very fine point (with an opening of less than 1 μm diameter) and filled with a good electrical conductor, such as a concentrated salt solution. This conductive core can then be connected to a voltmeter, such as an oscilloscope, to record the transmembrane voltage of the nerve cell.

The first type of electrical phenomenon can be observed as soon as a microelectrode is inserted through the membrane of the neuron. Upon entering the cell, the microelectrode reports a negative potential, indicating that neurons have a means of generating a constant voltage across their membranes when at rest. This voltage, called the **resting membrane potential**, depends on the type of neuron being examined, but it is always a fraction of a volt (typically –40 to –90 mV).

The electrical signals produced by neurons are caused by responses to stimuli, which then change the resting membrane potential. **Receptor potentials** are due to the activation of sensory neurons by external stimuli, such as light, sound, or heat. For example, touching the skin activates Pacinian corpuscles, receptor neurons that sense mechanical disturbances of the skin. These neurons respond to touch with a receptor potential that changes the resting potential for a fraction of a second (Figure 2.1A). These transient

Figure 2.1 Types of neuronal electrical signals. In all cases, microelectrodes are used to measure changes in the resting membrane potential during the indicated signals. (A) A brief touch causes a receptor potential in a Pacinian corpuscle in the skin. (B) Activation of a synaptic contact onto a hippocampal pyramidal neuron elicits a synaptic potential. (C) Stimulation of a spinal reflex produces an action potential in a spinal motor neuron.


(A) Receptor potential
Record
Membrane potential (mV)
–50
–60
Touch skin
Time (ms)
(B) Synaptic potential
Record
Stimulate
–60
–70
Activate synapse
Membrane potential (mV)
Time (ms)
(C) Action potential
Stimulate
Record
40
–60
Activate motor neuron
Membrane potential (mV)
Time (ms)

changes in potential are the first step in generating the sensation of vibrations (or "tickles") of the skin in the somatic sensory system (Chapter 8). Similar sorts of receptor potentials are observed in all other sensory neurons during transduction of sensory signals (Unit II).

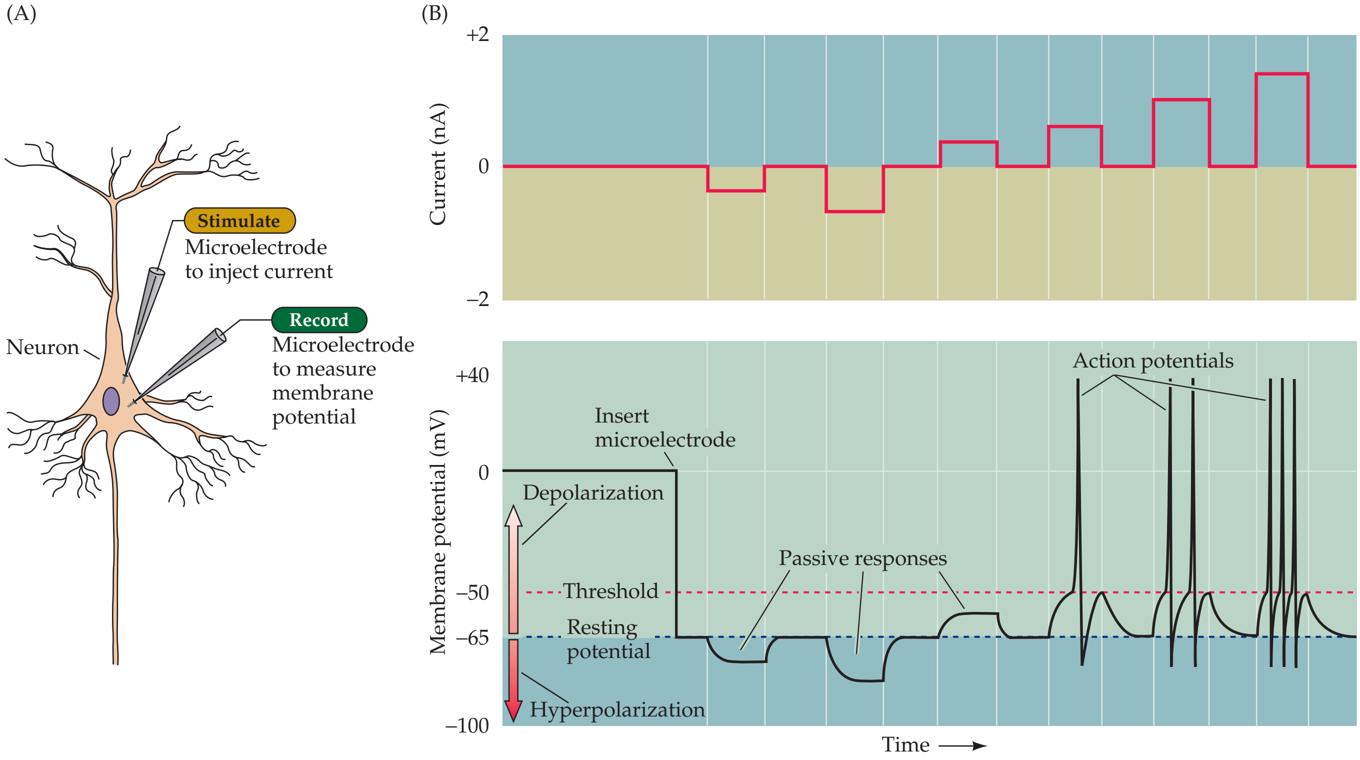
Another type of electrical signal is associated with communication between neurons at synaptic contacts. Activation of these synapses generates **synaptic potentials**, which allow transmission of information from one neuron to another. An example of such a signal is shown in Figure 2.1B. In this case, activation of a synaptic terminal innervating a hippocampal pyramidal neuron causes a very brief change in the resting membrane potential in the pyramidal neuron. Synaptic potentials serve as the means of exchanging information in complex neural circuits in both the central and peripheral nervous systems (Chapter 5).

The use of electrical signals—as in sending electricity over wires to provide power or information—presents a series of problems in electrical engineering. A fundamental problem for neurons is that their axons, which can be quite long (remember that a spinal motor neuron can extend for a meter or more), are not good electrical conductors. Although neurons and wires are both capable of passively conducting electricity, the electrical properties of neurons compare poorly to an ordinary wire. To compensate for this deficiency, neurons have evolved a “booster system” that allows them to conduct electrical signals over great distances despite their intrinsically poor electrical characteristics. The electrical signals produced by this booster system are called **action potentials** (which are also referred to as “spikes” or “impulses”). An example of an action potential recorded from the axon of a spinal motor neuron is shown in Figure 2.1C.

One way to elicit an action potential is to pass electrical current across the membrane of the neuron. In normal circumstances, this current would be generated by receptor potentials or by synaptic potentials. In the laboratory, however, electrical current suitable for initiating an action potential can be readily produced by inserting a second microelectrode into the same neuron and then connecting the electrode to a battery (Figure 2.2A). If the current delivered in this way makes the membrane potential more negative (**hyperpolarization**), nothing very dramatic happens. The membrane potential simply changes in proportion to the magnitude of the injected current (central part of Figure 2.2B). Such hyperpolarizing responses do not require any unique property of neurons and are therefore called passive electrical responses. A much more interesting phenomenon is seen if current of the opposite polarity is delivered, so that the membrane potential of the nerve cell becomes more positive than the resting potential (**depolarization**). In this case, at a certain level of membrane potential, called the **threshold potential**, an action potential occurs (see right side of Figure 2.2B).

The action potential, which is an active response generated by the neuron, is a brief (about 1 ms) change from negative to positive in the transmem-

Figure 2.2 Recording passive and active electrical signals in a nerve cell. (A) Two microelectrodes are inserted into a neuron; one of these measures membrane potential while the other injects current into the neuron. (B) Inserting the voltage-measuring microelectrode into the neuron reveals a negative potential, the resting membrane potential. Injecting current through the current-passing microelectrode alters the neuronal membrane potential. Hyperpolarizing current pulses produce only passive changes in the membrane potential. While small depolarizing currents also elict only passive responses, depolarizations that cause the membrane potential to meet or exceed threshold additionally evoke action potentials. Action potentials are active responses in the sense that they are generated by changes in the permeability of the neuronal membrane.



brane potential. Importantly, the amplitude of the action potential is independent of the magnitude of the current used to evoke it; that is, larger currents do not elicit larger action potentials. The action potentials of a given neuron are therefore said to be *all-or-none*, because they occur fully or not at all. If the amplitude or duration of the stimulus current is increased sufficiently, multiple action potentials occur, as can be seen in the responses to the three different current intensities shown in Figure 2.2B (right side). It follows, therefore, that the intensity of a stimulus is encoded in the frequency of action potentials rather than in their amplitude. This arrangement differs dramatically from receptor potentials, whose amplitudes are graded in proportion to the magnitude of the sensory stimulus, or synaptic potentials, whose amplitude varies according to the number of synapses activated and the previous amount of synaptic activity.

Because electrical signals are the basis of information transfer in the nervous system, it is essential to understand how these signals arise. Remarkably, all of the neuronal electrical signals described above are produced by similar mechanisms that rely upon the movement of ions across the neuronal membrane. The remainder of this chapter addresses the question of how nerve cells use ions to generate electrical potentials. Chapter 3 explores more specifically the means by which action potentials are produced and how these signals solve the problem of long-distance electrical conduction within nerve cells. Chapter 4 examines the properties of membrane molecules responsible for electrical signaling. Finally, Chapters 5–7 consider how electrical signals are transmitted from one nerve cell to another at synaptic contacts.

How Ionic Movements Produce Electrical Signals

Electrical potentials are generated across the membranes of neurons—and, indeed, all cells—because (1) there are *differences in the concentrations* of specific ions across nerve cell membranes, and (2) the membranes are *selectively permeable* to some of these ions. These two facts depend in turn on two different kinds of proteins in the cell membrane (Figure 2.3). The ion concentration gradients are established by proteins known as **active transporters**, which, as their name suggests, actively move ions into or out of cells against their concentration gradients. The selective permeability of membranes is

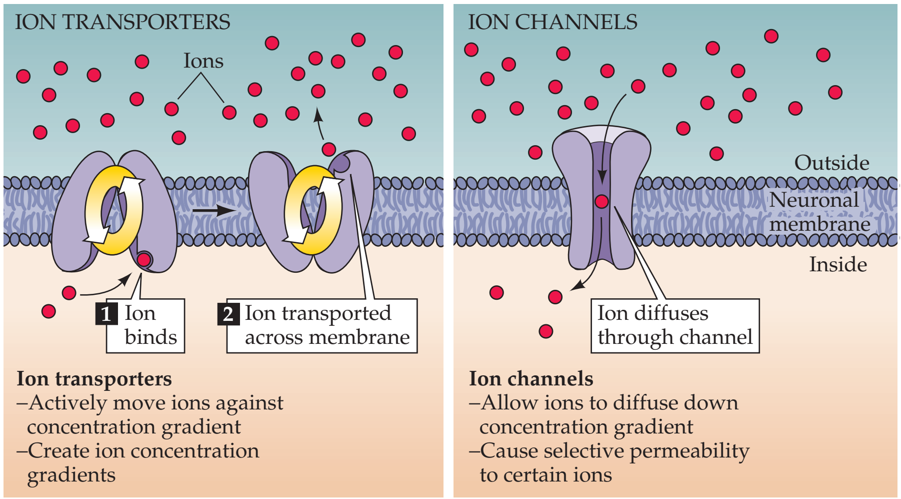

ION TRANSPORTERS
Ions
1 Ion binds
2 Ion transported across membrane
Ion transporters
–Actively move ions against concentration gradient
–Create ion concentration gradients
ION CHANNELS
Outside
Neuronal membrane
Inside
Ion diffuses through channel
Ion channels
–Allow ions to diffuse down concentration gradient
–Cause selective permeability to certain ions

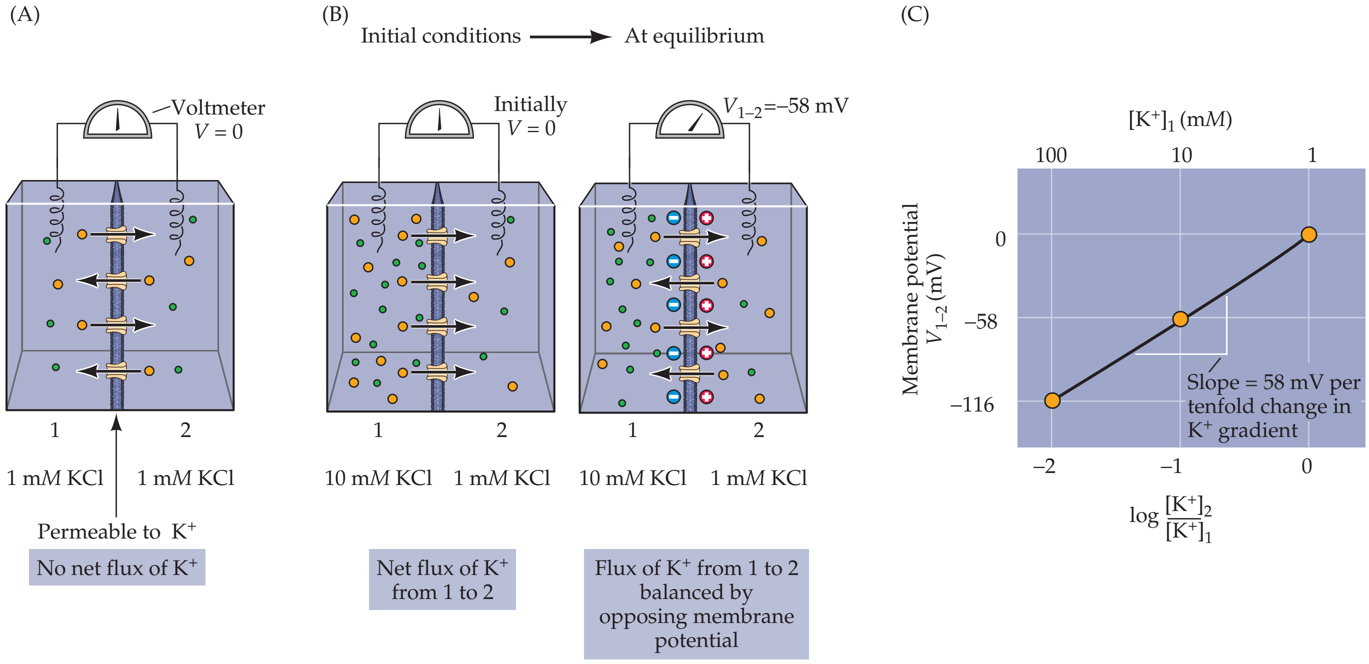
Figure 2.3 Ion transporters and ion channels are responsible for ionic movements across neuronal membranes. Transporters create ion concentration differences by actively transporting ions against their chemical gradients. Channels take advantage of these concentration gradients, allowing selected ions to move, via diffusion, down their chemical gradients.

due largely to **ion channels**, proteins that allow only certain kinds of ions to cross the membrane in the direction of their concentration gradients. Thus, channels and transporters basically work against each other, and in so doing they generate the resting membrane potential, action potentials, and the synaptic potentials and receptor potentials that trigger action potentials. The structure and function of these channels and transporters are described in Chapter 4.

To appreciate the role of ion gradients and selective permeability in generating a membrane potential, consider a simple system in which an artificial membrane separates two compartments containing solutions of ions. In such a system, it is possible to determine the composition of the two solutions and, thereby, control the ion gradients across the membrane. For example, take the case of a membrane that is permeable only to potassium ions (K^+). If the concentration of K^+ on each side of this membrane is equal, then no electrical potential will be measured across it (Figure 2.4A). However, if the concentration of K^+ is not the same on the two sides, then an electrical potential will be generated. For instance, if the concentration of K^+ on one side of the membrane (compartment 1) is 10 times higher than the K^+ concentration on the other side (compartment 2), then the electrical potential of compartment 1 will be negative relative to compartment 2 (Figure 2.4B). This difference in electrical potential is generated because the potassium ions flow down their concentration gradient and take their electrical charge (one positive charge per ion) with them as they go. Because neuronal membranes contain pumps that accumulate K^+ in the cell cytoplasm, and because potassium-permeable channels in the plasma membrane allow a transmembrane flow of K^+, an analogous situation exists in living nerve cells. A continual resting efflux of K^+ is therefore responsible for the resting membrane potential.

In the hypothetical case just described, an equilibrium will quickly be reached. As K^+ moves from compartment 1 to compartment 2 (the initial conditions on the left of Figure 2.4B), a potential is generated that tends to impede further flow of K^+. This impediment results from the fact that the

Figure 2.4 Electrochemical equilibrium. (A) A membrane permeable only to K^+ (yellow spheres) separates compartments 1 and 2, which contain the indicated concentrations of KCl. (B) Increasing the KCl concentration in compartment 1 to 10 m*M* initially causes a small movement of K^+ into compartment 2 (initial conditions) until the electromotive force acting on K^+ balances the concentration gradient, and the net movement of K^+ becomes zero (at equilibrium). (C) The relationship between the transmembrane concentration gradient ($[K^+]_2/[K^+]_1$) and the membrane potential. As predicted by the Nernst equation, this relationship is linear when plotted on semi-logarithmic coordinates, with a slope of 58 mV per tenfold difference in the concentration gradient.


(A)
Voltmeter
$V = 0$
1
2
1 m*M* KCl
1 m*M* KCl
Permeable to K^+
No net flux of K^+
(B)
Initial conditions → At equilibrium
Initially
$V = 0$
V_{1-2}=–58 mV
1
2
10 m*M* KCl
1 m*M* KCl
1
2
10 m*M* KCl
1 m*M* KCl
Net flux of K^+ from 1 to 2
Flux of K^+ from 1 to 2 balanced by opposing membrane potential
(C)
$[K^+]_1$ (m*M*)
100
10
1
Membrane potential V_{1-2} (mV)
0
–58
–116
Slope = 58 mV per tenfold change in K^+ gradient
–2
–1
0
$\log \frac{[K^+]_2}{[K^+]_1}$

potential gradient across the membrane tends to repel the positive potassium ions that would otherwise move across the membrane. Thus, as compartment 2 becomes positive relative to compartment 1, the increasing positivity makes compartment 2 less attractive to the positively charged K^+. The net movement (or flux) of K^+ will stop at the point (at equilibrium on the right of Figure 2.4B) where the potential change across the membrane (the relative positivity of compartment 2) exactly offsets the concentration gradient (the tenfold excess of K^+ in compartment 1). At this **electrochemical equilibrium**, there is an exact balance between two opposing forces: (1) the concentration gradient that causes K^+ to move from compartment 1 to compartment 2, taking along positive charge, and (2) an opposing electrical gradient that increasingly tends to stop K^+ from moving across the membrane (Figure 2.4B). The number of ions that needs to flow to generate this electrical potential is very small (approximately 10^{-12} moles of K^+ per cm^2 of membrane, or 10^{12} K^+ ions). This last fact is significant in two ways. First, it means that the concentrations of permeant ions on each side of the membrane remain essentially constant, even after the flow of ions has generated the potential. Second, the tiny fluxes of ions required to establish the membrane potential do not disrupt chemical electroneutrality because each ion has an oppositely charged counter-ion (chloride ions in the example shown in Figure 2.4) to maintain the neutrality of the solutions on each side of the membrane. The concentration of K^+ remains equal to the concentration of Cl^- in the solutions in compartments 1 and 2, meaning that the separation of charge that creates the potential difference is restricted to the immediate vicinity of the membrane.

The Forces That Create Membrane Potentials

The electrical potential generated across the membrane at electrochemical equilibrium, the **equilibrium potential**, can be predicted by a simple formula called the **Nernst equation**. This relationship is generally expressed as

$$E_X = \frac{RT}{zF} \ln \frac{[X]_2}{[X]_1}$$

where E_X is the equilibrium potential for any ion X, R is the gas constant, T is the absolute temperature (in degrees on the Kelvin scale), z is the valence (electrical charge) of the permeant ion, and F is the Faraday constant (the amount of electrical charge contained in one mole of a univalent ion). The brackets indicate the concentrations of ion X on each side of the membrane and the symbol ln indicates the natural logarithm of the concentration gradient. Because it is easier to perform calculations using base 10 logarithms and to perform experiments at room temperature, this relationship is usually simplified to

$$E_X = \frac{58}{z} \log \frac{[X]_2}{[X]_1}$$

where log indicates the base 10 logarithm of the concentration ratio. Thus, for the example in Figure 2.4B, the potential across the membrane at electrochemical equilibrium is

$$E_K = \frac{58}{z} \log \frac{[K]_2}{[K]_1} = 58 \log \frac{1}{10} = -58 \text{ mV}$$

The equilibrium potential is conventionally defined in terms of the potential difference between the reference compartment, side 2 in Figure 2.4, and the other side. This approach is also applied to biological systems. In this case, the outside of the cell is the conventional reference point (defined as zero potential). Thus, when the concentration of K^+ is higher inside than out, an inside-negative potential is measured across the K^+-permeable neuronal membrane.

For a simple hypothetical system with only one permeant ion species, the Nernst equation allows the electrical potential across the membrane at equilibrium to be predicted exactly. For example, if the concentration of K^+ on side 1 is increased to 100 m*M*, the membrane potential will be –116 mV. More generally, if the membrane potential is plotted against the logarithm of the K^+ concentration gradient ($[K]_2/[K]_1$), the Nernst equation predicts a linear relationship with a slope of 58 mV (actually $58/z$) per tenfold change in the K^+ gradient (Figure 2.4C).

To reinforce and extend the concept of electrochemical equilibrium, consider some additional experiments on the influence of ionic species and ionic permeability that could be performed on the simple model system in Figure 2.4. What would happen to the electrical potential across the membrane (the potential of side 1 relative to side 2) if the potassium on side 2 were replaced with 10 m*M* sodium (Na^+) and the K^+ in compartment 1 were replaced by 1 m*M* Na^+? No potential would be generated, because no Na^+ could flow across the membrane (which was defined as being permeable only to K^+). However, if under these ionic conditions (10 times more Na^+ in compartment 2) the K^+-permeable membrane were to be magically replaced by a membrane permeable only to Na^+, a potential of +58 mV would be measured at equilibrium. If 10 m*M* calcium (Ca^{2+}) were present in compartment 2 and 1 m*M* Ca^{2+} in compartment 1, and a Ca^{2+}-selective membrane separated the two sides, what would happen to the membrane potential? A potential of +29 mV would develop, because the valence of calcium is +2. Finally, what would happen to the membrane potential if 10 m*M* Cl^- were present in compartment 1 and 1 m*M* Cl^- were present in compartment 2, with the two sides separated by a Cl^--permeable membrane? Because the valence of this anion is –1, the potential would again be +58 mV.

The balance of chemical and electrical forces at equilibrium means that the electrical potential can determine ionic fluxes across the membrane, just as the ionic gradient can determine the membrane potential. To examine the influence of membrane potential on ionic flux, imagine connecting a battery across the two sides of the membrane to control the electrical potential across the membrane without changing the distribution of ions on the two sides (Figure 2.5). As long as the battery is off, things will be just as in Figure 2.4, with the flow of K^+ from compartment 1 to compartment 2 causing a negative membrane potential (Figure 2.5A, left). However, if the battery is used to make compartment 1 initially more negative relative to compartment 2, there will be less K^+ flux, because the negative potential will tend to keep K^+ in compartment 1. How negative will side 1 need to be before there is no net flux of K^+? The answer is –58 mV, the voltage needed to counter the tenfold difference in K^+ concentrations on the two sides of the membrane (Figure 2.5A, center). If compartment 1 is initially made more negative than –58 mV, then K^+ will actually flow from compartment 2 into compartment 1, because the positive ions will be attracted to the more negative potential of compartment 1 (Figure 2.5A, right). This example demonstrates that both the direction and magnitude of ion flux depend on the membrane potential. Thus, in some circumstances the electrical potential can overcome an ionic concentration gradient.

The ability to alter ion flux experimentally by changing either the potential imposed on the membrane (Figure 2.5B) or the transmembrane concen-

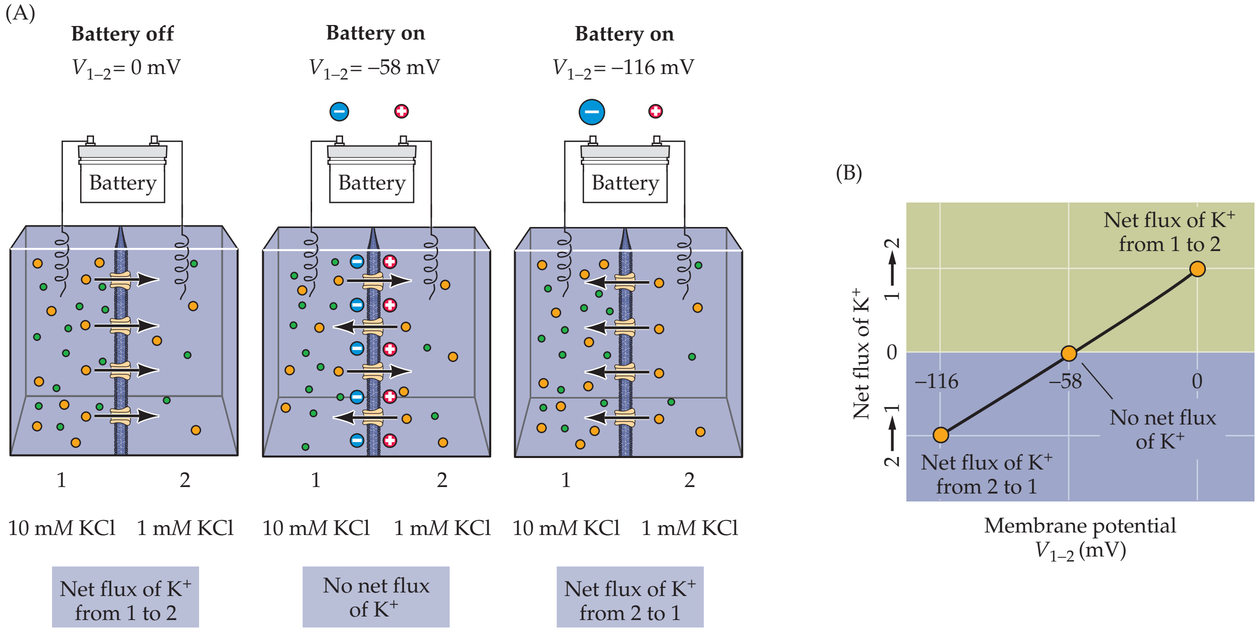

(A)
Battery off
V_{1-2} = 0 mV
Battery on
V_{1-2} = –58 mV
Battery on
V_{1-2} = –116 mV
Battery
Battery
Battery
1
2
1
2
1
2
10 mM KCl
1 mM KCl
10 mM KCl
1 mM KCl
10 mM KCl
1 mM KCl
Net flux of K+ from 1 to 2
No net flux of K+
Net flux of K+ from 2 to 1
(B)
Net flux of K+ from 1 to 2
Net flux of K+
1 → 2
0
2 ← 1
–116
–58
0
No net flux of K+
Net flux of K+ from 2 to 1
Membrane potential V_{1-2} (mV)

Figure 2.5 Membrane potential influences ion fluxes. (A) Connecting a battery across the K^+-permeable membrane allows direct control of membrane potential. When the battery is turned off (left), K^+ ions (yellow) flow simply according to their concentration gradient. Setting the initial membrane potential (V_{1-2}) at the equilibrium potential for K^+ (center) yields no net flux of K^+, while making the membrane potential more negative than the K^+ equilibrium potential (right) causes K^+ to flow against its concentration gradient. (B) Relationship between membrane potential and direction of K^+ flux.

tration gradient for an ion (see Figure 2.4C) provides convenient tools for studying ion fluxes across the plasma membranes of neurons, as will be evident in many of the experiments described in the following chapters.

Electrochemical Equilibrium in an Environment with More Than One Permeant Ion

Now consider a somewhat more complex situation in which Na^+ and K^+ are unequally distributed across the membrane, as in Figure 2.6A. What would happen if 10 m*M* K^+ and 1 m*M* Na^+ were present in compartment 1, and 1 m*M* K^+ and 10 m*M* Na^+ in compartment 2? If the membrane were permeable only to K^+, the membrane potential would be –58 mV; if the membrane were permeable only to Na^+, the potential would be +58 mV. But what would the potential be if the membrane were permeable to both K^+ and Na^+? In this case, the potential would depend on the relative permeability of the membrane to K^+ and Na^+. If it were more permeable to K^+, the potential would approach –58 mV, and if it were more permeable to Na^+, the potential would be closer to +58 mV. Because there is no permeability term in the Nernst equation, which only considers the simple case of a single permeant ion species, a more elaborate equation is needed that takes into account both the concentration gradients of the permeant ions and the relative permeability of the membrane to each permeant species.

Such an equation was developed by David Goldman in 1943. For the case most relevant to neurons, in which K^+, Na^+, and Cl^- are the primary permeant ions, the **Goldman equation** is written

$$V = 58 \log \frac{P_{\mathrm{K}}[\mathrm{K}]_2 + P_{\mathrm{Na}}[\mathrm{Na}]_2 + P_{\mathrm{Cl}}[\mathrm{Cl}]_1}{P_{\mathrm{K}}[\mathrm{K}]_1 + P_{\mathrm{Na}}[\mathrm{Na}]_1 + P_{\mathrm{Cl}}[\mathrm{Cl}]_2}$$

where V is the voltage across the membrane (again, compartment 1 relative to the reference compartment 2) and P indicates the permeability of the

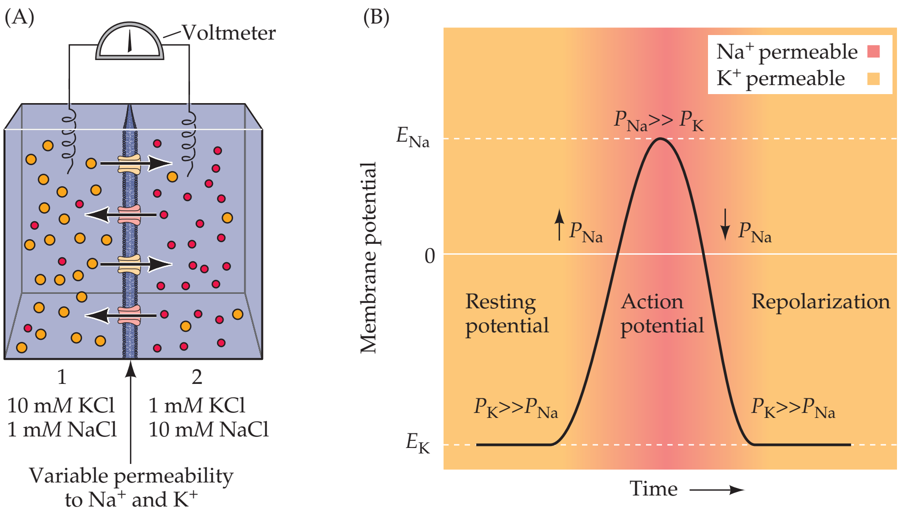


Figure 2.6 Resting and action potentials entail permeabilities to different ions. (A) Hypothetical situation in which a membrane variably permeable to Na^+ (red) and K^+ (yellow) separates two compartments that contain both ions. For simplicity, Cl^- ions are not shown in the diagram. (B) Schematic representation of the membrane ionic permeabilities associated with resting and action potentials. At rest, neuronal membranes are more permeable to K^+ (yellow) than to Na^+ (red); accordingly, the resting membrane potential is negative and approaches the equilibrium potential for K^+, E_K. During an action potential, the membrane becomes very permeable to Na^+ (red); thus the membrane potential becomes positive and approaches the equilibrium potential for Na^+, E_{Na}. The rise in Na^+ permeability is transient, however, so that the membrane again becomes primarily permeable to K^+ (yellow), causing the potential to return to its negative resting value. Notice that at the equilibrium potential for a given ion, there is no net flux of that ion across the membrane.

membrane to each ion of interest. The Goldman equation is thus an extended version of the Nernst equation that takes into account the relative permeabilities of each of the ions involved. The relationship between the two equations becomes obvious in the situation where the membrane is permeable only to one ion, say, K^+; in this case, the Goldman expression collapses back to the simpler Nernst equation. In this context, it is important to note that the valence factor (z) in the Nernst equation has been eliminated; this is why the concentrations of negatively charged chloride ions, Cl^-, have been inverted relative to the concentrations of the positively charged ions [remember that $-\log(A/B) = \log(B/A)$].

If the membrane in Figure 2.6A is permeable to K^+ and Na^+ only, the terms involving Cl^- drop out because P_{Cl} is 0. In this case, solution of the Goldman equation yields a potential of –58 mV when only K^+ is permeant, +58 mV when only Na^+ is permeant, and some intermediate value if both ions are permeant. For example, if K^+ and Na^+ were equally permeant, then the potential would be 0 mV.

With respect to neural signaling, it is particularly pertinent to ask what would happen if the membrane started out being permeable to K^+, and then temporarily switched to become most permeable to Na^+. In this circumstance, the membrane potential would start out at a negative level, become positive while the Na^+ permeability remained high, and then fall back to a negative level as the Na^+ permeability decreased again. As it turns out, this last case essentially describes what goes on in a neuron during the generation of an action potential. In the resting state, P_K of the neuronal plasma membrane is much higher than P_{Na}; since, as a result of the action of ion transporters, there is always more K^+ inside the cell than outside (Table 2.1), the resting potential is negative (Figure 2.6B). As the membrane potential is depolarized (by synaptic action, for example), P_{Na} increases. The transient increase in Na^+ permeability causes the membrane potential to become even more positive (red region in Figure 2.6B), because Na^+ rushes in (there is much more Na^+ outside a neuron than inside, again as a result of ion pumps). Because of this positive feedback loop, an action potential occurs. The rise in Na^+ permeability during the action potential is transient, however; as the membrane permeability to K^+ is restored, the membrane potential quickly returns to its resting level.

TABLE 2.1
Extracellular and Intracellular Ion Concentrations

	Concentration (mM)	
Ion	*Intracellular*	*Extracellular*
Squid neuron		
Potassium (K^+)	400	20
Sodium (Na^+)	50	440
Chloride (Cl^-)	40–150	560
Calcium (Ca^{2+})	0.0001	10
Mammalian neuron		
Potassium (K^+)	140	5
Sodium (Na^+)	5–15	145
Chloride (Cl^-)	4–30	110
Calcium (Ca^{2+})	0.0001	1–2

Armed with an appreciation of these simple electrochemical principles, it will be much easier to understand the following, more detailed account of how neurons generate resting and action potentials.

The Ionic Basis of the Resting Membrane Potential

The action of ion transporters creates substantial transmembrane gradients for most ions. Table 2.1 summarizes the ion concentrations measured directly in an exceptionally large nerve cell found in the nervous system of the squid (Box A). Such measurements are the basis for stating that there is much more K^+ inside the neuron than out, and much more Na^+ outside than in. Similar concentration gradients occur in the neurons of most animals, including humans. However, because the ionic strength of mammalian blood is lower than that of sea-dwelling animals such as squid, in mammals the concentrations of each ion are several times lower. These transporter-dependent concentration gradients are, indirectly, the source of the resting neuronal membrane potential and the action potential.

Once the ion concentration gradients across various neuronal membranes are known, the Nernst equation can be used to calculate the equilibrium potential for K^+ and other major ions. Since the resting membrane potential of the squid neuron is approximately –65 mV, K^+ is the ion that is closest to being in electrochemical equilibrium when the cell is at rest. This fact implies that the resting membrane is more permeable to K^+ than to the other ions listed in Table 2.1, and that this permeability is the source of resting potentials.

It is possible to test this guess, as Alan Hodgkin and Bernard Katz did in 1949, by asking what happens to the resting membrane potential if the concentration of K^+ outside the neuron is altered. If the resting membrane were permeable only to K^+, then the Goldman equation (or even the simpler Nernst equation) predicts that the membrane potential will vary in proportion to the logarithm of the K^+ concentration gradient across the membrane. Assuming that the internal K^+ concentration is unchanged during the experiment, a plot of membrane potential against the logarithm of the external K^+ concentration should yield a straight line with a slope of 58 mV per tenfold change in external K^+ concentration at room temperature (see Figure 2.4C). (The slope becomes about 61 mV at mammalian body temperatures.)

Box A

The Remarkable Giant Nerve Cells of Squid

Many of the initial insights into how ion concentration gradients and changes in membrane permeability produce electrical signals came from experiments performed on the extraordinarily large nerve cells of the squid. The axons of these nerve cells can be up to 1 mm in diameter—100 to 1000 times larger than mammalian axons. Thus, squid axons are large enough to allow experiments that would be impossible on most other nerve cells. For example, it is not difficult to insert simple wire electrodes inside these giant axons and make reliable electrical measurements. The relative ease of this approach yielded the first intracellular recordings of action potentials from nerve cells and, as discussed in the next chapter, the first experimental measurements of the ion currents that produce action potentials. It also is practical to extrude the cytoplasm from giant axons and measure its ionic composition (see Table 2.1). In addition, some giant nerve cells form synaptic contacts with other giant nerve cells, producing very large synapses that have been extraordinarily valuable in understanding the fundamental mechanisms of synaptic transmission (see Chapter 5).

Giant neurons evidently evolved in squid because they enhanced survival. These neurons participate in a simple neural circuit that activates the contraction of the mantle muscle, producing a jet propulsion effect that allows the squid to move away from predators at a remarkably fast speed. As discussed in Chapter 3, larger axonal diameter allows faster conduction of action potentials. Thus, presumably these huge nerve cells help squid escape more successfully from their numerous enemies.

Today—nearly 70 years after their discovery by John Z. Young at University College London—the giant nerve cells of squid remain useful experimental systems for probing basic neuronal functions.

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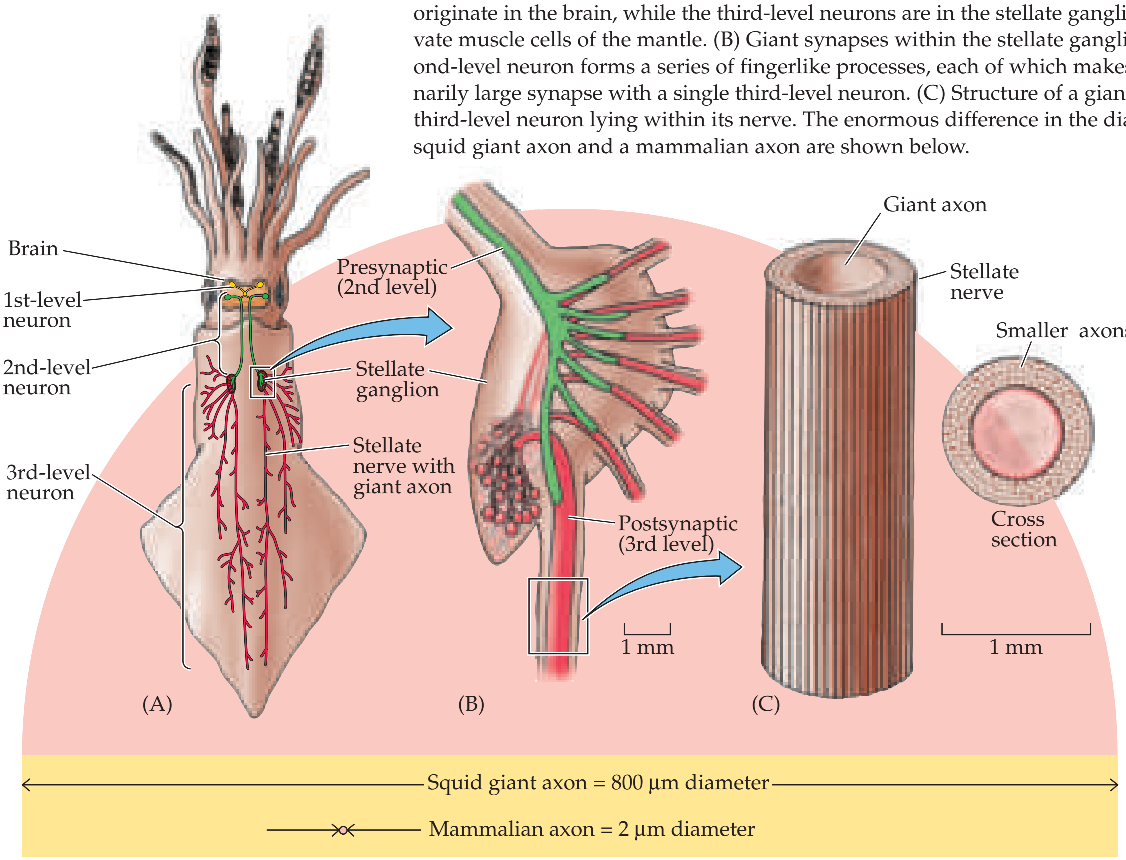
(A) Diagram of a squid, showing the location of its giant nerve cells. Different colors indicate the neuronal components of the escape circuitry. The first- and second-level neurons originate in the brain, while the third-level neurons are in the stellate ganglion and innervate muscle cells of the mantle. (B) Giant synapses within the stellate ganglion. The second-level neuron forms a series of fingerlike processes, each of which makes an extraordinarily large synapse with a single third-level neuron. (C) Structure of a giant axon of a third-level neuron lying within its nerve. The enormous difference in the diameters of a squid giant axon and a mammalian axon are shown below.



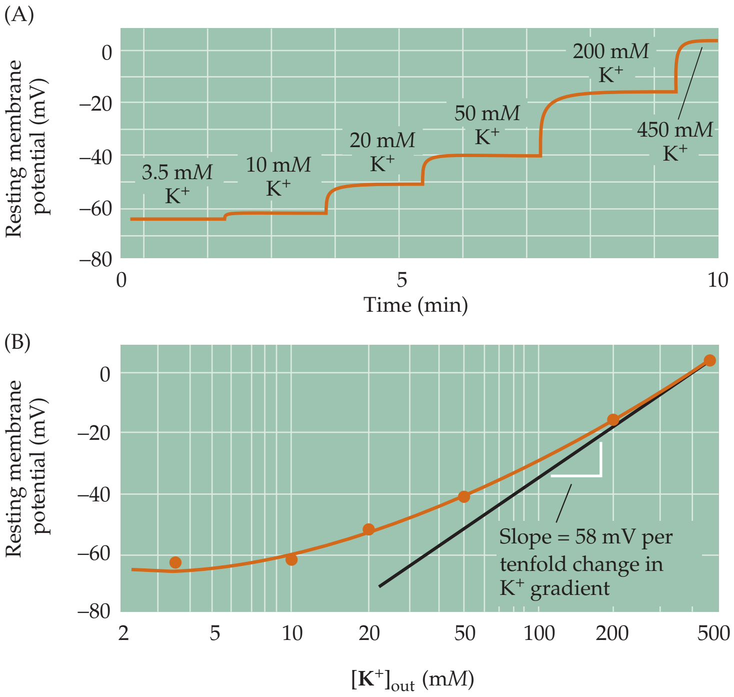


Figure 2.7 Experimental evidence that the resting membrane potential of a squid giant axon is determined by the K^+ concentration gradient across the membrane. (A) Increasing the external K^+ concentration makes the resting membrane potential more positive. (B) Relationship between resting membrane potential and external K^+ concentration, plotted on a semi-logarithmic scale. The straight line represents a slope of 58 mV per tenfold change in concentration, as given by the Nernst equation. (After Hodgkin and Katz, 1949.)

When Hodgkin and Katz carried out this experiment on a living squid neuron, they found that the resting membrane potential did indeed change when the external K^+ concentration was modified, becoming less negative as external K^+ concentration was raised (Figure 2.7A). When the external K^+ concentration was raised high enough to equal the concentration of K^+ inside the neuron, thus making the K^+ equilibrium potential 0 mV, the resting membrane potential was also approximately 0 mV. In short, the resting membrane potential varied as predicted with the logarithm of the K^+ concentration, with a slope that approached 58 mV per tenfold change in K^+ concentration (Figure 2.7B). The value obtained was not exactly 58 mV because other ions, such as Cl^- and Na^+, are also slightly permeable, and thus influence the resting potential to a small degree. The contribution of these other ions is particularly evident at low external K^+ levels, again as predicted by the Goldman equation. In general, however, manipulation of the external concentrations of these other ions has only a small effect, emphasizing that K^+ permeability is indeed the primary source of the resting membrane potential.

In summary, Hodgkin and Katz showed that the inside-negative resting potential arises because (1) the membrane of the resting neuron is more permeable to K^+ than to any of the other ions present, and (2) there is more K^+ inside the neuron than outside. The selective permeability to K^+ is caused by K^+-permeable membrane channels that are open in resting neurons, and the large K^+ concentration gradient is, as noted, produced by membrane transporters that selectively accumulate K^+ within neurons. Many subsequent studies have confirmed the general validity of these principles.

The Ionic Basis of Action Potentials

What causes the membrane potential of a neuron to depolarize during an action potential? Although a general answer to this question has been given (increased permeability to Na^+), it is well worth examining some of the experimental support for this concept. Given the data presented in Table 2.1, one can use the Nernst equation to calculate that the equilibrium potential for Na^+ (E_{Na}) in neurons, and indeed in most cells, is positive. Thus, if the membrane were to become highly permeable to Na^+, the membrane potential would approach E_{Na}. Based on these considerations, Hodgkin and Katz hypothesized that the action potential arises because the neuronal membrane becomes temporarily permeable to Na^+.

Taking advantage of the same style of ion substitution experiment they used to assess the resting potential, Hodgkin and Katz tested the role of Na^+ in generating the action potential by asking what happens to the action potential when Na^+ is removed from the external medium. They found that lowering the external Na^+ concentration reduces both the rate of rise of the action potential and its peak amplitude (Figure 2.8A–C). Indeed, when they examined this Na^+ dependence quantitatively, they found a more-or-less linear relationship between the amplitude of the action potential and the logarithm of the external Na^+ concentration (Figure 2.8D). The slope of this rela-

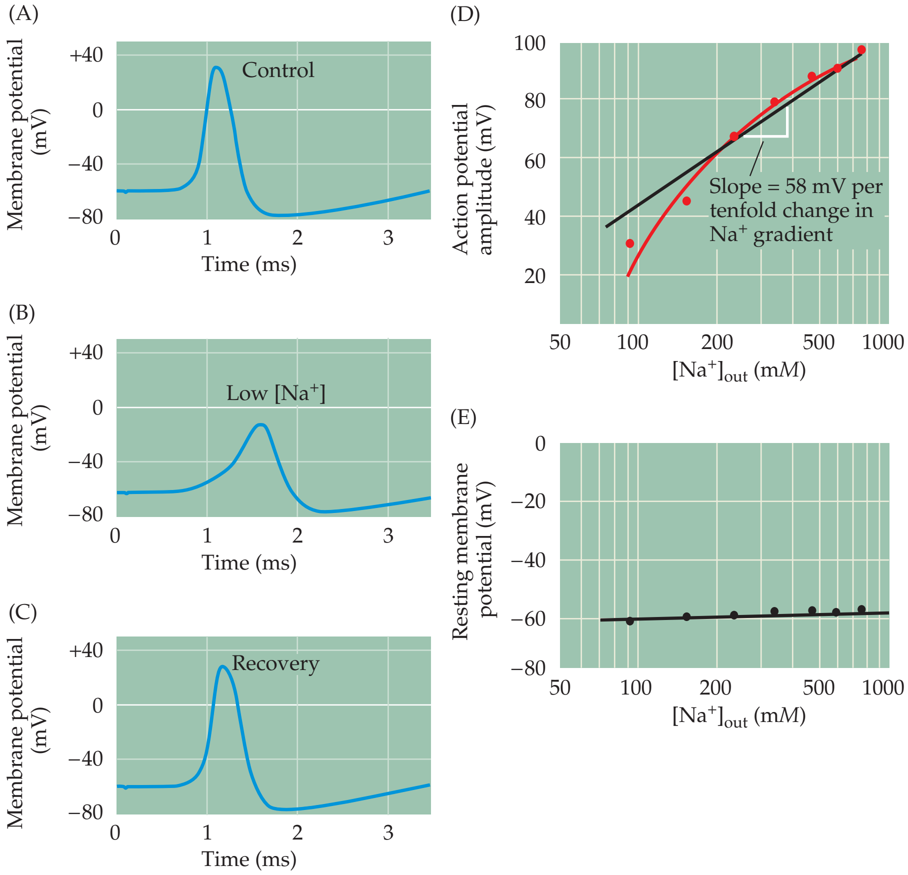


Figure 2.8 The role of sodium in the generation of an action potential in a squid giant axon. (A) An action potential evoked with the normal ion concentrations inside and outside the cell. (B) The amplitude and rate of rise of the action potential diminish when external sodium concentration is reduced to one-third of normal, but (C) recover when the Na^+ is replaced. (D) While the amplitude of the action potential is quite sensitive to the external concentration of Na^+, the resting membrane potential (E) is little affected by changing the concentration of this ion. (After Hodgkin and Katz, 1949.)

Box B

Action Potential Form and Nomenclature

The action potential of the squid giant axon has a characteristic shape, or waveform, with a number of different phases (Figure A). During the rising phase, the membrane potential rapidly depolarizes. In fact, action potentials cause the membrane potential to depolarize so much that the membrane potential transiently becomes positive with respect to the external medium, producing an overshoot. The overshoot of the action potential gives way to a falling phase in which the membrane potential rapidly repolarizes. Repolarization takes the membrane potential to levels even more negative than the resting membrane potential for a short time; this brief period of hyperpolarization is called the undershoot.

Although the waveform of the squid action potential is typical, the details of the action potential form vary widely from neuron to neuron in different animals. In myelinated axons of vertebrate motor neurons (Figure B), the action potential is virtually indistinguishable from that of the squid axon. However, the action potential recorded in the cell body of this same motor neuron (Figure C) looks rather different. Thus, the action potential waveform can vary even within the same neuron. More complex action potentials are seen in other central neurons. For example, action potentials recorded from the cell bodies of neurons in the mammalian inferior olive (a region of the brainstem involved in motor control) last tens of milliseconds (Figure D). These action potentials exhibit a pronounced plateau during their falling phase, and their undershoot lasts even longer than that of the motor neuron. One of the most dramatic types of action potentials occurs in the cell bodies of cerebellar Purkinje neurons (Figure E). These potentials have several complex phases that result from the summation of multiple, discrete action potentials.

The variety of action potential waveforms could mean that each type of neuron has a different mechanism of action potential production. Fortunately, however, these diverse waveforms all result from relatively minor variations in the scheme used by the squid giant axon. For example, plateaus in the repolarization phase result from the presence of ion channels that are permeable to Ca^{2+}, and long-lasting undershoots result from the presence of additional types of membrane K^+ channels. The complex action potential of the Purkinje cell results from these extra features plus the fact that different types of action potentials are generated in various parts of the Purkinje neuron—cell body, dendrites, and axons—and are summed together in recordings from the cell body. Thus, the lessons learned from the squid axon are applicable to, and indeed essential for, understanding action potential generation in all neurons.

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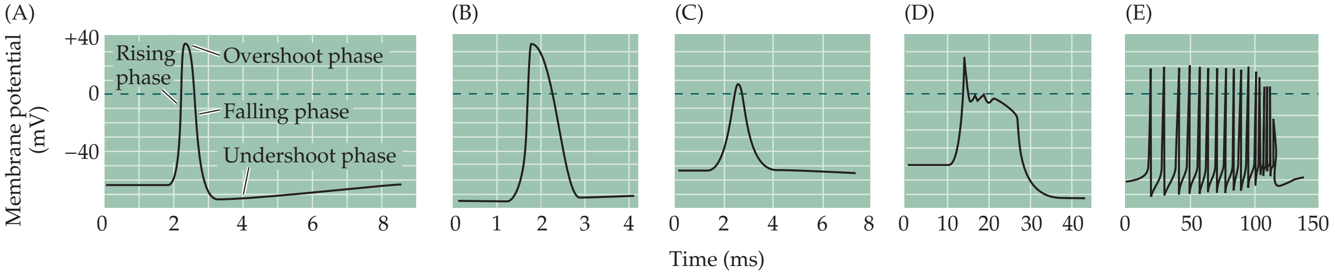
(A) The phases of an action potential of the squid giant axon. (B) Action potential recorded from a myelinated axon of a frog motor neuron. (C) Action potential recorded from the cell body of a frog motor neuron. The action potential is smaller and the undershoot prolonged in comparison to the action potential recorded from the axon of this same neuron (B). (D) Action potential recorded from the cell body of a neuron from the inferior olive of a guinea pig. This action potential has a pronounced plateau during its falling phase. (E) Action potential recorded from the cell body of a Purkinje neuron in the cerebellum of a guinea pig. (A after Hodgkin and Huxley, 1939; B after Dodge and Frankenhaeuser, 1958; C after Barrett and Barrett, 1976; D after Llinás and Yarom, 1981; E after Llinás and Sugimori, 1980.)



tionship approached a value of 58 mV per tenfold change in Na^+ concentration, as expected for a membrane selectively permeable to Na^+. In contrast, lowering Na^+ concentration had very little effect on the resting membrane potential (Figure 2.8E). Thus, while the resting neuronal membrane is only slightly permeable to Na^+, the membrane becomes extraordinarily permeable to Na^+ during the **rising phase** and **overshoot phase** of the action potential (see Box B for an explanation of action potential nomenclature). This temporary increase in Na^+ permeability results from the opening of Na^+-selective channels that are essentially closed in the resting state. Membrane pumps maintain a large electrochemical gradient for Na^+, which is in much higher concentration outside the neuron than inside. When the Na^+ channels open, Na^+ flows into the neuron, causing the membrane potential to depolarize and approach E_{Na}.

The time that the membrane potential lingers near E_{Na} (about +58 mV) during the overshoot phase of an action potential is brief because the increased membrane permeability to Na^+ itself is short-lived. The membrane potential rapidly repolarizes to resting levels and is actually followed by a transient **undershoot**. As will be described in Chapter 3, these latter events in the action potential are due to an inactivation of the Na^+ permeability and an increase in the K^+ permeability of the membrane. During the undershoot, the membrane potential is transiently hyperpolarized because K^+ permeability becomes even greater than it is at rest. The action potential ends when this phase of enhanced K^+ permeability subsides, and the membrane potential thus returns to its normal resting level.

The ion substitution experiments carried out by Hodgkin and Katz provided convincing evidence that the resting membrane potential results from a high resting membrane permeability to K^+, and that depolarization during an action potential results from a transient rise in membrane Na^+ permeability. Although these experiments identified the ions that flow during an action potential, they did not establish *how* the neuronal membrane is able to change its ionic permeability to generate the action potential, or what mechanisms trigger this critical change. The next chapter addresses these issues, documenting the surprising conclusion that the neuronal membrane potential itself affects membrane permeability.

Summary

Nerve cells generate electrical signals to convey information over substantial distances and to transmit it to other cells by means of synaptic connections. These signals ultimately depend on changes in the resting electrical potential across the neuronal membrane. A resting potential occurs because nerve cell membranes are permeable to one or more ion species subject to an electrochemical gradient. More specifically, a negative membrane potential at rest results from a net efflux of K^+ across neuronal membranes that are predominantly permeable to K^+. In contrast, an action potential occurs when a transient rise in Na^+ permeability allows a net flow of Na^+ in the opposite direction across the membrane that is now predominantly permeable to Na^+. The brief rise in membrane Na^+ permeability is followed by a secondary, transient rise in membrane K^+ permeability that repolarizes the neuronal membrane and produces a brief undershoot of the action potential. As a result of these processes, the membrane is depolarized in an all-or-none fashion during an action potential. When these active permeability changes subside, the membrane potential returns to its resting level because of the high resting membrane permeability to K^+.

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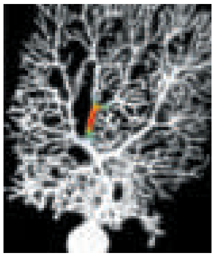
Chapter 3



Voltage-Dependent Membrane Permeability

Overview

The action potential, the primary electrical signal generated by nerve cells, reflects changes in membrane permeability to specific ions. Present understanding of these changes in ionic permeability is based on evidence obtained by the voltage clamp technique, which permits detailed characterization of permeability changes as a function of membrane potential and time. For most types of axons, these changes consist of a rapid and transient rise in sodium (Na^+) permeability, followed by a slower but more prolonged rise in potassium (K^+) permeability. Both permeabilities are voltage-dependent, increasing as the membrane potential depolarizes. The kinetics and voltage dependence of Na^+ and K^+ permeabilities provide a complete explanation of action potential generation. Depolarizing the membrane potential to the threshold level causes a rapid, self-sustaining increase in Na^+ permeability that produces the rising phase of the action potential; however, the Na^+ permeability increase is short-lived and is followed by a slower increase in K^+ permeability that restores the membrane potential to its usual negative resting level. A mathematical model that describes the behavior of these ionic permeabilities predicts virtually all of the observed properties of action potentials. Importantly, this same ionic mechanism permits action potentials to be propagated along the length of neuronal axons, explaining how electrical signals are conveyed throughout the nervous system.

Ionic Currents Across Nerve Cell Membranes

The previous chapter introduced the idea that nerve cells generate electrical signals by virtue of a membrane that is differentially permeable to various ion species. In particular, a transient increase in the permeability of the neuronal membrane to Na^+ initiates the action potential. This chapter considers exactly how this increase in Na^+ permeability occurs. A key to understanding this phenomenon is the observation that action potentials are initiated *only* when the neuronal membrane potential becomes more positive than a threshold level. This observation suggests that the mechanism responsible for the increase in Na^+ permeability is sensitive to the membrane potential. Therefore, if one could understand how a change in membrane potential activates Na^+ permeability, it should be possible to explain how action potentials are generated.

The fact that the Na^+ permeability that generates the membrane potential change is itself sensitive to the membrane potential presents both conceptual and practical obstacles to studying the mechanism of the action potential. A practical problem is the difficulty of systematically varying the membrane

Box A

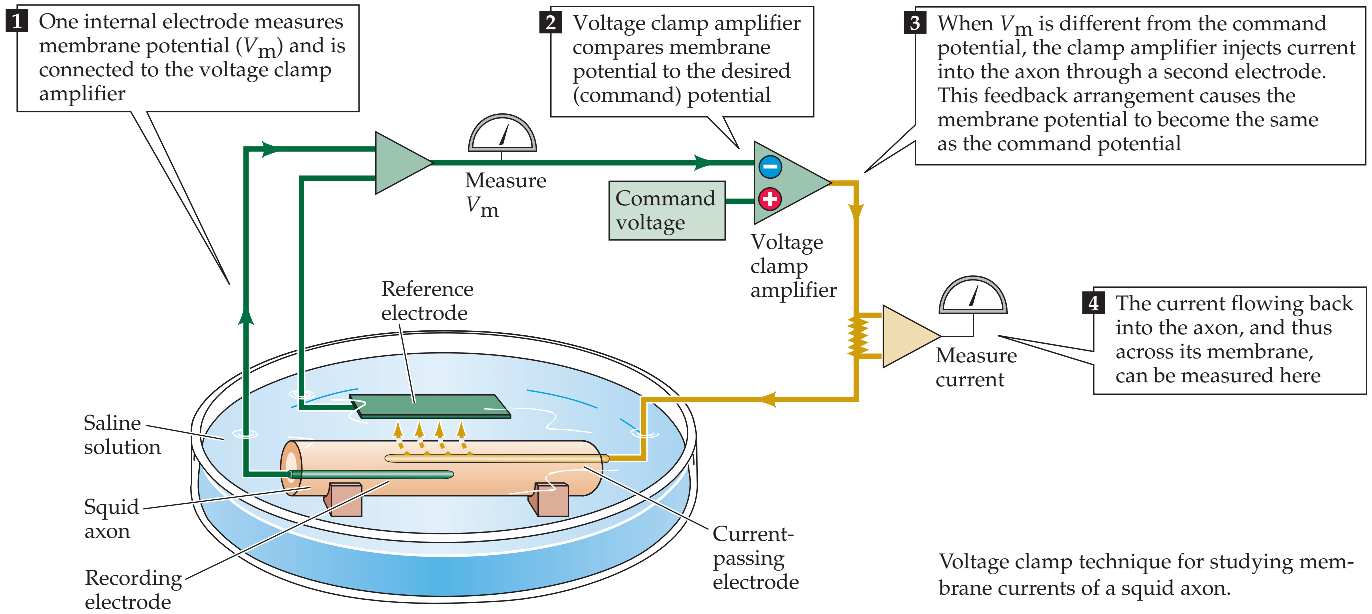
The Voltage Clamp Method

Breakthroughs in scientific research often rely on the development of new technologies. In the case of the action potential, detailed understanding came only after of the invention of the voltage clamp technique by Kenneth Cole in the 1940s. This device is called a voltage clamp because it controls, or clamps, membrane potential (or voltage) at any level desired by the experimenter. The method measures the membrane potential with a microelectrode (or other type of electrode) placed inside the cell (1), and electronically compares this voltage to the voltage to be maintained (called the *command voltage*) (2). The clamp circuitry then passes a current back into the cell though another intracellular electrode (3). This electronic feedback circuit holds the membrane potential at the desired level, even in the face of permeability changes that would normally alter the membrane potential (such as those generated during the action potential). Most importantly, the device permits the simultaneous measurement of the current needed to keep the cell at a given voltage (4). This current is exactly equal to the amount of current flowing across the neuronal membrane, allowing direct measurement of these membrane currents. Therefore, the voltage clamp technique can indicate how membrane potential influences ionic current flow across the membrane. This information gave Hodgkin and Huxley the key insights that led to their model for action potential generation.

Today, the voltage clamp method remains widely used to study ionic currents in neurons and other cells. The most popular contemporary version of this approach is the patch clamp technique, a method that can be applied to virtually any cell and has a resolution high enough to measure the minute electrical currents flowing through single ion channels (see Box A in Chapter 4).

References

COLE, K. S. (1968) *Membranes, Ions and Impulses: A Chapter of Classical Biophysics*. Berkeley, CA: University of California Press.


1 One internal electrode measures membrane potential (V_{m}) and is connected to the voltage clamp amplifier
2 Voltage clamp amplifier compares membrane potential to the desired (command) potential
3 When V_{m} is different from the command potential, the clamp amplifier injects current into the axon through a second electrode. This feedback arrangement causes the membrane potential to become the same as the command potential
Measure V_{m}
Command voltage
Voltage clamp amplifier
Reference electrode
Measure current
4 The current flowing back into the axon, and thus across its membrane, can be measured here
Saline solution
Squid axon
Recording electrode
Current-passing electrode

Voltage clamp technique for studying membrane currents of a squid axon.

potential to study the permeability change, because such changes in membrane potential will produce an action potential, which causes further, uncontrolled changes in the membrane potential. Historically, then, it was not really possible to understand action potentials until a technique was developed that allowed experimenters to control membrane potential *and* simultaneously measure the underlying permeability changes. This technique, the **voltage clamp method** (Box A), provides the information needed to define the ionic permeability of the membrane at any level of membrane potential.

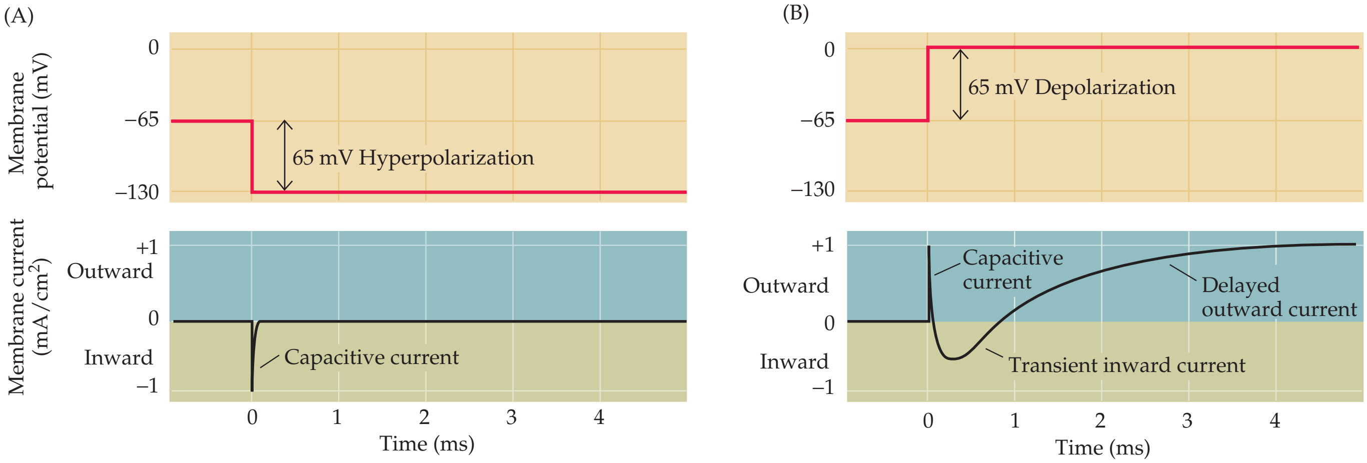
In the late 1940s, Alan Hodgkin and Andrew Huxley working at the University of Cambridge used the voltage clamp technique to work out the permeability changes underlying the action potential. They again chose to use the giant neuron of the squid because its large size (up to 1 mm in diameter; see Box A in Chapter 2) allowed insertion of the electrodes necessary for voltage clamping. They were the first investigators to test directly the hypothesis that potential-sensitive Na^+ and K^+ permeability changes are both necessary and sufficient for the production of action potentials.

Hodgkin and Huxley's first goal was to determine whether neuronal membranes do, in fact, have voltage-dependent permeabilities. To address this issue, they asked whether ionic currents flow across the membrane when its potential is changed. The result of one such experiment is shown in Figure 3.1. Figure 3.1A illustrates the currents produced by a squid axon when its membrane potential, V_m, is hyperpolarized from the resting level of –65 mV to –130 mV. The initial response of the axon results from the redistribution of charge across the axonal membrane. This capacitive current is nearly instantaneous, ending within a fraction of a millisecond. Aside from this brief event, very little current flows when the membrane is hyperpolarized. However, when the membrane potential is depolarized from –65 mV to 0 mV, the response is quite different (Figure 3.1B). Following the capacitive current, the axon produces a rapidly rising inward ionic current (inward refers to a positive charge entering the cell—that is, cations in or anions out), which gives way to a more slowly rising, delayed outward current. The fact that membrane depolarization elicits these ionic currents establishes that the membrane permeability of axons is indeed voltage-dependent.

Two Types of Voltage-Dependent Ionic Current

The results shown in Figure 3.1 demonstrate that the ionic permeability of neuronal membranes is voltage-sensitive, but the experiments do not identify how many types of permeability exist, or which ions are involved. As discussed in Chapter 2 (see Figure 2.5), varying the potential across a membrane makes it possible to deduce the equilibrium potential for the ionic fluxes through the membrane, and thus to identify the ions that are flowing.

Figure 3.1 Current flow across a squid axon membrane during a voltage clamp experiment. (A) A 65 mV hyperpolarization of the membrane potential produces only a very brief capacitive current. (B) A 65 mV depolarization of the membrane potential also produces a brief capacitive current, which is followed by a longer lasting but transient phase of inward current and a delayed but sustained outward current. (After Hodgkin et al., 1952.)



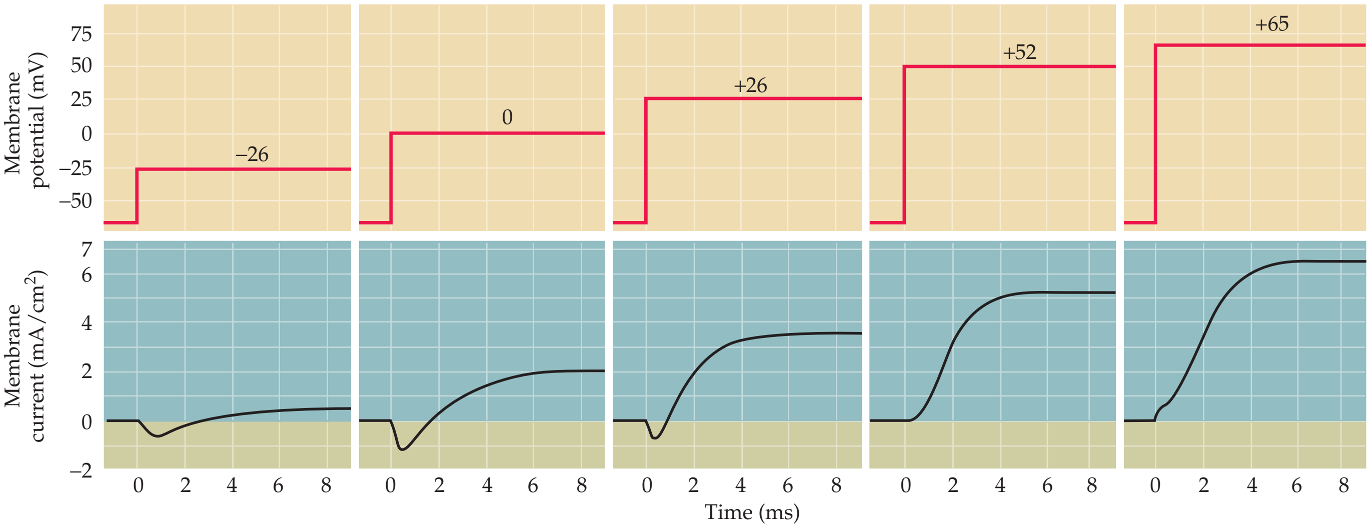


Figure 3.2 Current produced by membrane depolarizations to several different potentials. The early current first increases, then decreases in magnitude as the depolarization increases; note that this current is actually reversed in polarity at potentials more positive than about +55 mV. In contrast, the late current increases monotonically with increasing depolarization. (After Hodgkin et al., 1952.)

Because the voltage clamp method allows the membrane potential to be changed while ionic currents are being measured, it was a straightforward matter for Hodgkin and Huxley to determine ionic permeability by examining how the properties of the early inward and late outward currents changed as the membrane potential was varied (Figure 3.2). As already noted, no appreciable ionic currents flow at membrane potentials more negative than the resting potential. At more positive potentials, however, the currents not only flow but change in magnitude. The early current has a U-shaped dependence on membrane potential, increasing over a range of depolarizations up to approximately 0 mV but decreasing as the potential is depolarized further. In contrast, the late current increases monotonically with increasingly positive membrane potentials. These different responses to membrane potential can be seen more clearly when the magnitudes of the two current components are plotted as a function of membrane potential, as in Figure 3.3.

The voltage sensitivity of the early inward current gives an important clue about the nature of the ions carrying the current, namely, that no current flows when the membrane potential is clamped at +52 mV. For the squid neurons studied by Hodgkin and Huxley, the external Na^+ concentration is 440 m*M*, and the internal Na^+ concentration is 50 m*M*. For this concentration gradient, the Nernst equation predicts that the equilibrium poten-

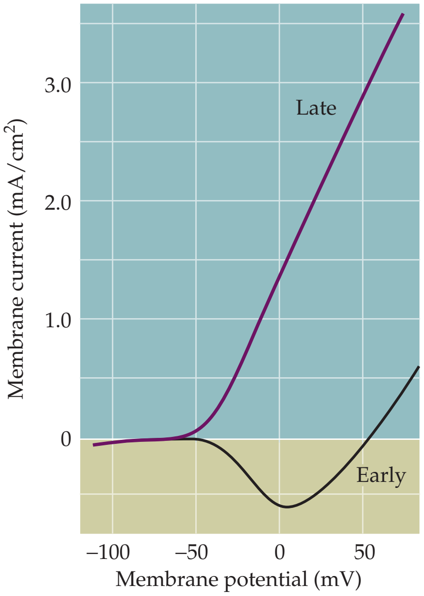
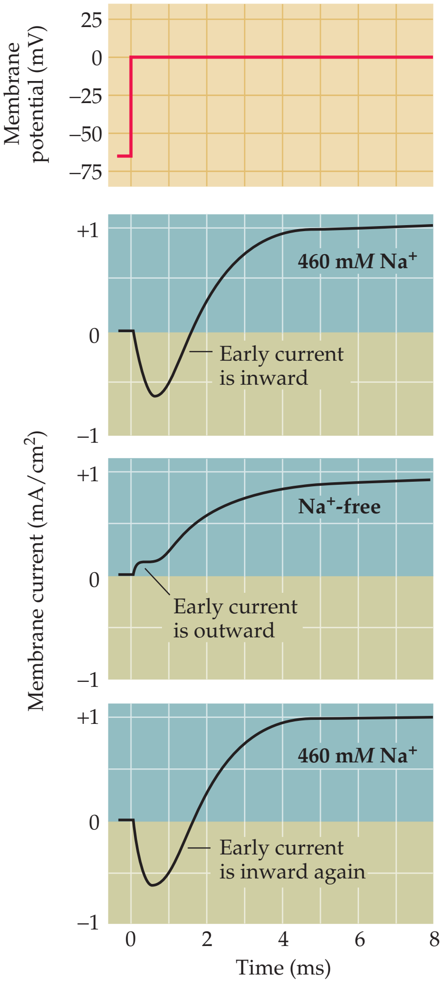


Figure 3.3 Relationship between current amplitude and membrane potential, taken from experiments such as the one shown in Figure 3.2. Whereas the late outward current increases steeply with increasing depolarization, the early inward current first increases in magnitude, but then decreases and reverses to outward current at about +55 mV (the sodium equilibrium potential). (After Hodgkin et al., 1952.)

Figure 3.4 Dependence of the early inward current on sodium. In the presence of normal external concentrations of Na^+, depolarization of a squid axon to 0 mV produces an inward initial current. However, removal of external Na^+ causes the initial inward current to become outward, an effect that is reversed by restoration of external Na^+. (After Hodgkin and Huxley, 1952a.)



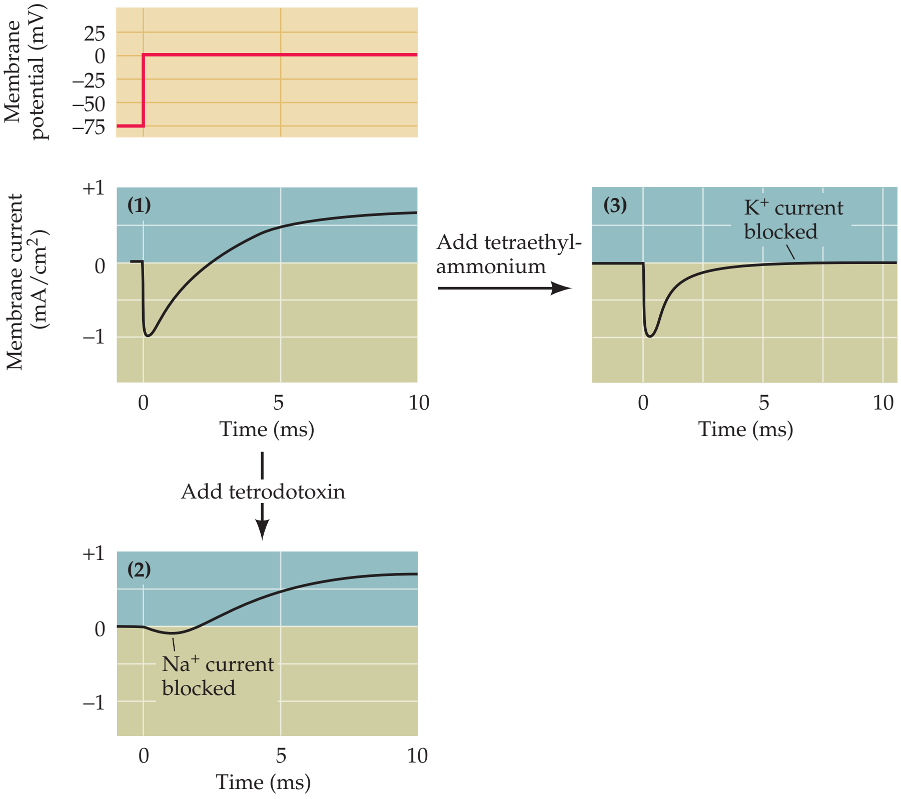
tial for Na^+ should be +55 mV. Recall further from Chapter 2 that at the Na^+ equilibrium potential there is no net flux of Na^+ across the membrane, even if the membrane is highly permeable to Na^+. Thus, the experimental observation that no current flows at the membrane potential where Na^+ cannot flow is a strong indication that the early inward current is carried by entry of Na^+ into the axon.

An even more demanding way to test whether Na^+ carries the early inward current is to examine the behavior of this current after removing external Na^+. Removing the Na^+ outside the axon makes E_{Na} negative; if the permeability to Na^+ is increased under these conditions, current should flow outward as Na^+ leaves the neuron, due to the reversed electrochemical gradient. When Hodgkin and Huxley performed this experiment, they obtained the result shown in Figure 3.4. Removing external Na^+ caused the early inward current to reverse its polarity and become an outward current at a membrane potential that gave rise to an inward current when external Na^+ was present. This result demonstrates convincingly that the early inward current measured when Na^+ is present in the external medium must be due to Na^+ entering the neuron.

Notice that removal of external Na^+ in the experiment shown in Figure 3.4 has little effect on the outward current that flows after the neuron has been kept at a depolarized membrane voltage for several milliseconds. This further result shows that the late outward current must be due to the flow of an ion other than Na^+. Several lines of evidence presented by Hodgkin, Huxley, and others showed that this late outward current is caused by K^+ exiting the neuron. Perhaps the most compelling demonstration of K^+ involvement is that the amount of K^+ efflux from the neuron, measured by loading the neuron with radioactive K^+, is closely correlated with the magnitude of the late outward current.

Taken together, these experiments using the voltage clamp show that changing the membrane potential to a level more positive than the resting potential produces two effects: an early influx of Na^+ into the neuron, followed by a delayed efflux of K^+. The early influx of Na^+ produces a transient inward current, whereas the delayed efflux of K^+ produces a sustained outward current. The differences in the time course and ionic selectivity of the two fluxes suggest that two different ionic permeability mechanisms are activated by changes in membrane potential. Confirmation that there are indeed two distinct mechanisms has come from pharmacological studies of drugs that specifically affect these two currents (Figure 3.5). **Tetrodotoxin**, an alkaloid neurotoxin found in certain puffer fish, tropical frogs, and salamanders, blocks the Na^+ current without affecting the K^+ current. Conversely, **tetraethylammonium ions** block K^+ currents without affecting Na^+ currents. The differential sensitivity of Na^+ and K^+ currents to these drugs provides strong additional evidence that Na^+ and K^+ flow through independent permeability pathways. As discussed in Chapter 4, it is now known that these pathways are ion channels that are selectively permeable to either Na^+ or K^+. In fact, tetrodotoxin, tetraethylammonium, and other drugs that interact with spe-

Figure 3.5 Pharmacological separation of Na^+ and K^+ currents into sodium and potassium components. Panel (1) shows the current that flows when the membrane potential of a squid axon is depolarized to 0 mV in control conditions. (2) Treatment with tetrodotoxin causes the early Na^+ currents to disappear but spares the late K^+ currents. (3) Addition of tetraethylammonium blocks the K^+ currents without affecting the Na^+ currents. (After Moore et al., 1967 and Armstrong and Binstock, 1965.)



cific types of ion channels have been extraordinarily useful tools in characterizing these channel molecules (see Chapter 4).

Two Voltage-Dependent Membrane Conductances

The next goal Hodgkin and Huxley set for themselves was to describe Na^+ and K^+ permeability changes mathematically. To do this, they assumed that the ionic currents are due to a change in **membrane conductance**, defined as the reciprocal of the membrane resistance. Membrane conductance is thus closely related, although not identical, to membrane permeability. When evaluating ionic movements from an electrical standpoint, it is convenient to describe them in terms of ionic conductances rather than ionic permeabilities. For present purposes, permeability and conductance can be considered synonymous. If membrane conductance (g) obeys Ohm's Law (which states that voltage is equal to the product of current and resistance), then the ionic current that flows during an increase in membrane conductance is given by

$$I_{ion} = g_{ion}\,(V_m - E_{ion})$$

where I_{ion} is the ionic current, V_m is the membrane potential, and E_{ion} is the equilibrium potential for the ion flowing through the conductance, g_{ion}. The difference between V_m and E_{ion} is the electrochemical driving force acting on the ion.

Hodgkin and Huxley used this simple relationship to calculate the dependence of Na^+ and K^+ conductances on time and membrane potential. They knew V_m, which was set by their voltage clamp device (Figure 3.6A), and could determine E_{Na} and E_K from the ionic concentrations on the two sides

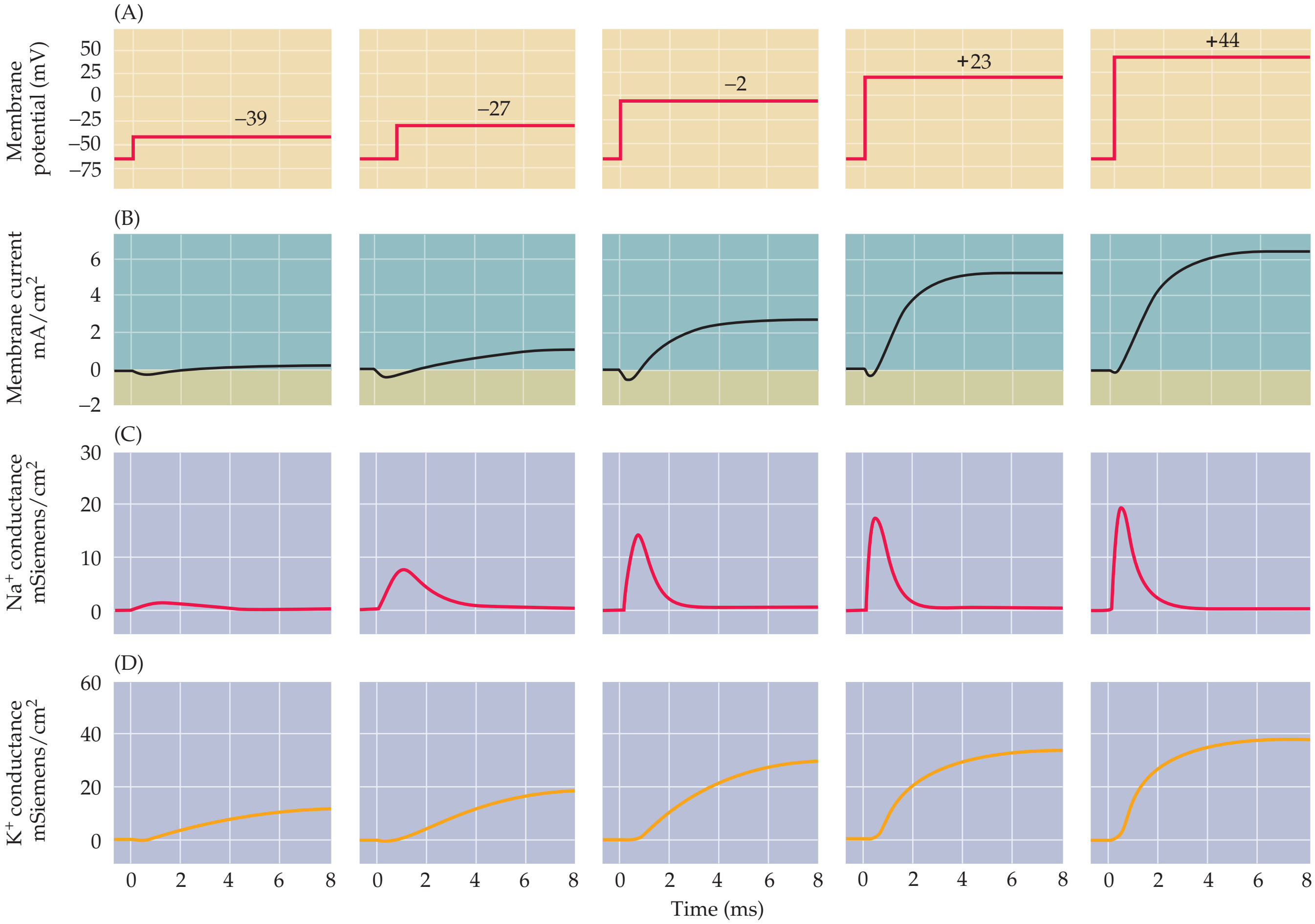


Figure 3.6 Membrane conductance changes underlying the action potential are time- and voltage-dependent. Depolarizations to various membrane potentials (A) elicit different membrane currents (B). Below are shown the Na$^+$ (C) and K$^+$ (D) conductances calculated from these currents. Both peak Na$^+$ conductance and steady-state K$^+$ conductance increase as the membrane potential becomes more positive. In addition, the activation of both conductances, as well as the rate of inactivation of the Na$^+$ conductance, occur more rapidly with larger depolarizations. (After Hodgkin and Huxley, 1952b.)

of the axonal membrane (see Table 2.1). The currents carried by Na$^+$ and K$^+$—I_{Na} and I_K—could be determined separately from recordings of the membrane currents resulting from depolarization (Figure 3.6B) by measuring the difference between currents recorded in the presence and absence of external Na$^+$ (as shown in Figure 3.4). From these measurements, Hodgkin and Huxley were able to calculate g_{Na} and g_K (Figure 3.6C,D), from which they drew two fundamental conclusions. The first conclusion is that the Na$^+$ and K$^+$ conductances change over time. For example, both Na$^+$ and K$^+$ conductances require some time to **activate**, or turn on. In particular, the K$^+$ conductance has a pronounced delay, requiring several milliseconds to reach its maximum (Figure 3.6D), whereas the Na$^+$ conductance reaches its maximum more rapidly (Figure 3.6C). The more rapid activation of the Na$^+$ conductance allows the resulting inward Na$^+$ current to precede the delayed outward K$^+$ current (see Figure 3.6B). Although the Na$^+$ conductance rises rapidly, it quickly declines, even though the membrane potential is kept at a depolarized level. This fact shows that depolarization not only causes the Na$^+$ conductance to activate, but also causes it to decrease over time, or **inactivate**. The K$^+$ conductance of the squid axon does not inactivate in this way; thus, while the Na$^+$ and K$^+$ conductances share the property of time-dependent activation, only the Na$^+$ conductance inactivates. (Inactivating K$^+$ conductances have since been discovered in other types of nerve cells; see Chapter 4.) The time courses of the Na$^+$ and K$^+$ conductances are voltage-

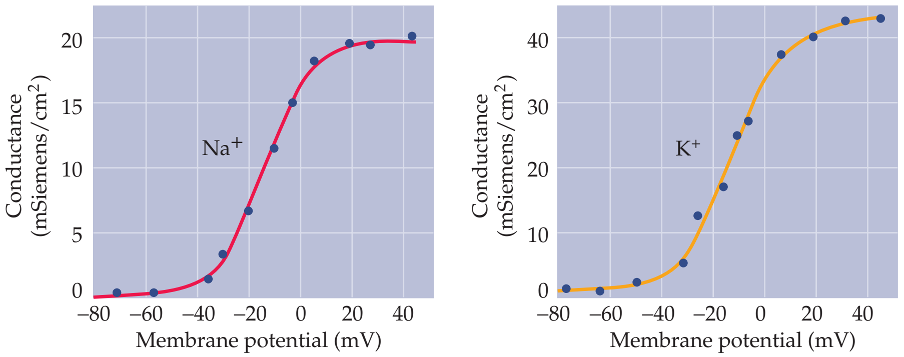


Figure 3.7 Depolarization increases Na$^+$ and K$^+$ conductances of the squid giant axon. The peak magnitude of Na$^+$ conductance and steady-state value of K$^+$ conductance both increase steeply as the membrane potential is depolarized. (After Hodgkin and Huxley, 1952b.)

dependent, with the speed of both activation and inactivation increasing at more depolarized potentials. This finding accounts for more rapid time courses of membrane currents measured at more depolarized potentials.

The second conclusion derived from Hodgkin and Huxley's calculations is that both the Na$^+$ and K$^+$ conductances are voltage-dependent—that is, both conductances increase progressively as the neuron is depolarized. Figure 3.7 illustrates this by plotting the relationship between peak value of the conductances (from Figure 3.6C,D) against the membrane potential. Note the similar voltage dependence for each conductance; both conductances are quite small at negative potentials, maximal at very positive potentials, and exquisitely dependent on membrane voltage at intermediate potentials. The observation that these conductances are sensitive to changes in membrane potential shows that the mechanism underlying the conductances somehow "senses" the voltage across the membrane.

All told, the voltage clamp experiments carried out by Hodgkin and Huxley showed that the ionic currents that flow when the neuronal membrane is depolarized are due to three different voltage-sensitive processes: (1) activation of Na$^+$ conductance, (2) activation of K$^+$ conductance, and (3) inactivation of Na$^+$ conductance.

Reconstruction of the Action Potential

From their experimental measurements, Hodgkin and Huxley were able to construct a detailed mathematical model of the Na$^+$ and K$^+$ conductance changes. The goal of these modeling efforts was to determine whether the Na$^+$ and K$^+$ conductances alone are sufficient to produce an action potential. Using this information, they could in fact generate the form and time course of the action potential with remarkable accuracy (Figure 3.8A). Further, the Hodgkin-Huxley model predicted other features of action potential behavior in the squid axon, such as how the delay before action potential generation changes in response to stimulating currents of different intensities (Figure 3.8B,C). The model also predicted that the axon membrane would become refractory to further excitation for a brief period following an action potential, as was experimentally observed.

The Hodgkin-Huxley model also provided many insights into how action potentials are generated. Figure 3.8A shows a reconstructed action potential, together with the time courses of the underlying Na$^+$ and K$^+$ conductances. The coincidence of the initial increase in Na$^+$ conductance with the rapid rising phase of the action potential demonstrates that a selective increase in

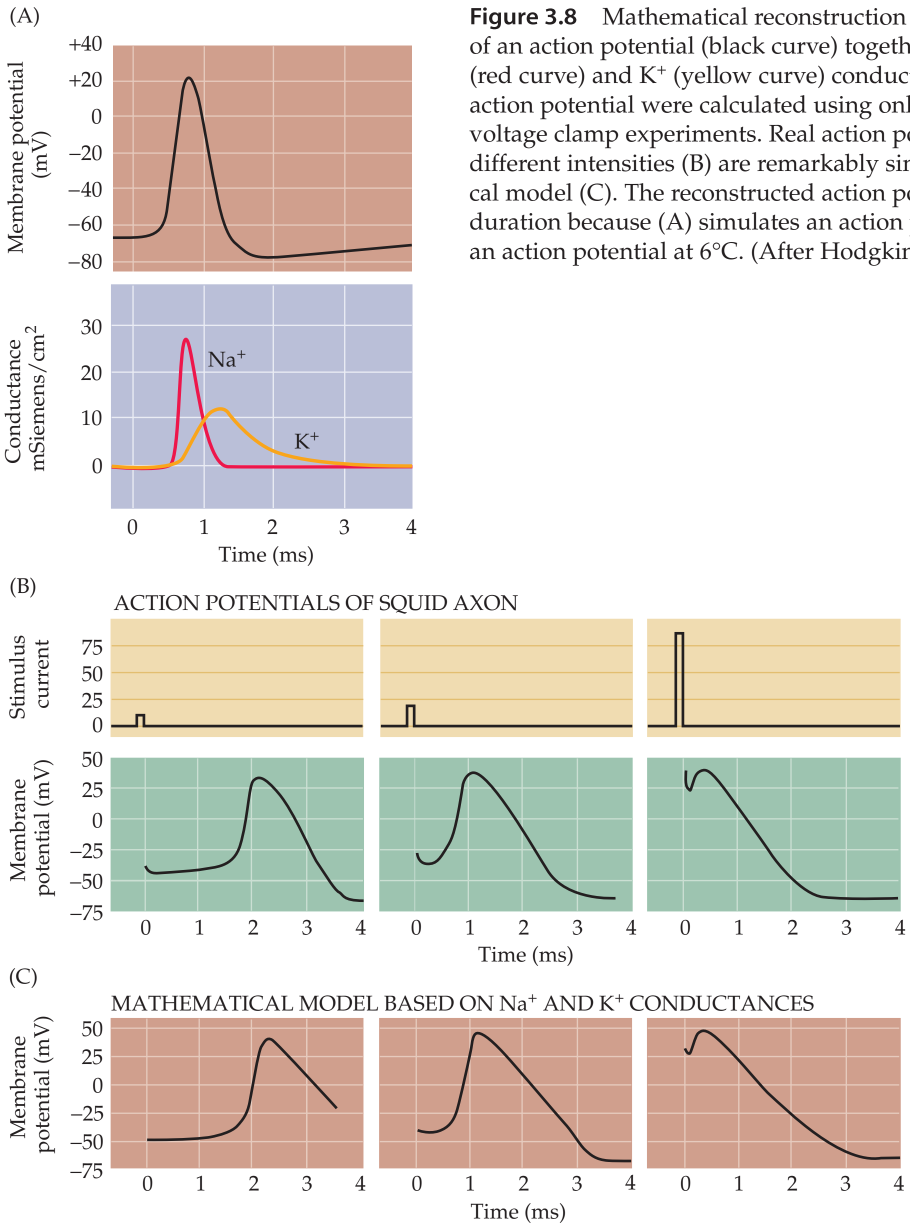


Figure 3.8 Mathematical reconstruction of the action potential. (A) Reconstruction of an action potential (black curve) together with the underlying changes in Na^+ (red curve) and K^+ (yellow curve) conductance. The size and time course of the action potential were calculated using only the properties of g_{Na} and g_K measured in voltage clamp experiments. Real action potentials evoked by brief current pulses of different intensities (B) are remarkably similar to those generated by the mathematical model (C). The reconstructed action potentials shown in (A) and (C) differ in duration because (A) simulates an action potential at 19°C, whereas (C) simulates an action potential at 6°C. (After Hodgkin and Huxley, 1952d.)

Na^+ conductance is responsible for action potential initiation. The increase in Na^+ conductance causes Na^+ to enter the neuron, thus depolarizing the membrane potential, which approaches E_{Na}. The rate of depolarization subsequently falls both because the electrochemical driving force on Na^+ decreases and because the Na^+ conductance inactivates. At the same time, depolarization slowly activates the voltage-dependent K^+ conductance, causing K^+ to leave the cell and repolarizing the membrane potential toward E_K. Because the K^+ conductance becomes temporarily higher than it is in the resting condition, the membrane potential actually becomes briefly more negative than the normal resting potential (the **undershoot**). The hyperpolarization of the membrane potential causes the voltage-dependent K^+ conductance (and any Na^+ conductance not inactivated) to turn off, allowing the membrane potential to return to its resting level.

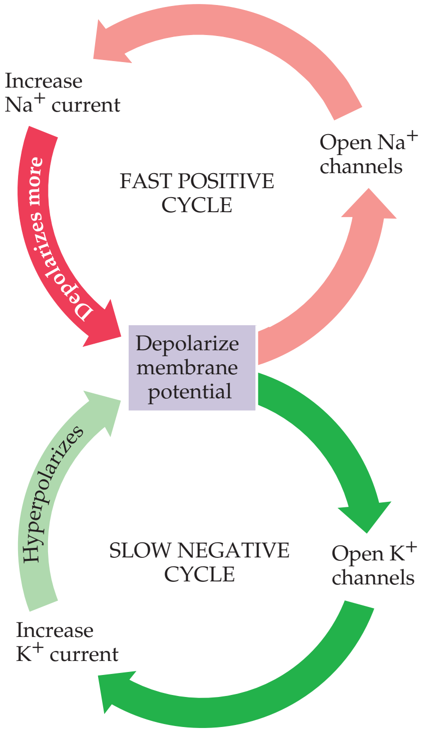


Figure 3.9 Feedback cycles responsible for membrane potential changes during an action potential. Membrane depolarization rapidly activates a positive feedback cycle fueled by the voltage-dependent activation of Na$^+$ conductance. This phenomenon is followed by the slower activation of a negative feedback loop as depolarization activates a K$^+$ conductance, which helps to repolarize the membrane potential and terminate the action potential.

This mechanism of action potential generation represents a positive feedback loop: Activating the voltage-dependent Na$^+$ conductance increases Na$^+$ entry into the neuron, which makes the membrane potential depolarize, which leads to the activation of still more Na$^+$ conductance, more Na$^+$ entry, and still further depolarization (Figure 3.9). Positive feedback continues unabated until Na$^+$ conductance inactivation and K$^+$ conductance activation restore the membrane potential to the resting level. Because this positive feedback loop, once initiated, is sustained by the intrinsic properties of the neuron—namely, the voltage dependence of the ionic conductances—the action potential is self-supporting, or **regenerative**. This regenerative quality explains why action potentials exhibit all-or-none behavior (see Figure 2.1), and why they have a threshold (Box B). The delayed activation of the K$^+$ conductance represents a negative feedback loop that eventually restores the membrane to its resting state.

Hodgkin and Huxley's reconstruction of the action potential and all its features shows that the properties of the voltage-sensitive Na$^+$ and K$^+$ conductances, together with the electrochemical driving forces created by ion transporters, are sufficient to explain action potentials. Their use of both empirical and theoretical methods brought an unprecedented level of rigor to a long-standing problem, setting a standard of proof that is achieved only rarely in biological research.

Long-Distance Signaling by Means of Action Potentials

The voltage-dependent mechanisms of action potential generation also explain the long-distance transmission of these electrical signals. Recall from Chapter 2 that neurons are relatively poor conductors of electricity, at least compared to a wire. Current conduction by wires, and by neurons in the absence of action potentials, is called **passive current flow** (Box C). The passive electrical properties of a nerve cell axon can be determined by measuring the voltage change resulting from a current pulse passed across the axonal membrane (Figure 3.10A). If this current pulse is not large enough to generate action potentials, the magnitude of the resulting potential change decays exponentially with increasing distance from the site of current injection (Figure 3.10B). Typically, the potential falls to a small fraction of its initial value at a distance of no more than a couple of millimeters away from the site of injection (Figure 3.10C). The progressive decrease in the amplitude of the induced potential change occurs because the injected current leaks out across the axonal membrane; accordingly, less current is available to change the membrane potential farther along the axon. Thus, the leakiness of the axonal membrane prevents effective passive transmission of electrical signals in all but the shortest axons (those 1 mm or less in length). Likewise, the leakiness of the membrane slows the time course of the responses measured at increasing distances from the site where current was injected (Figure 3.10D).

Box B

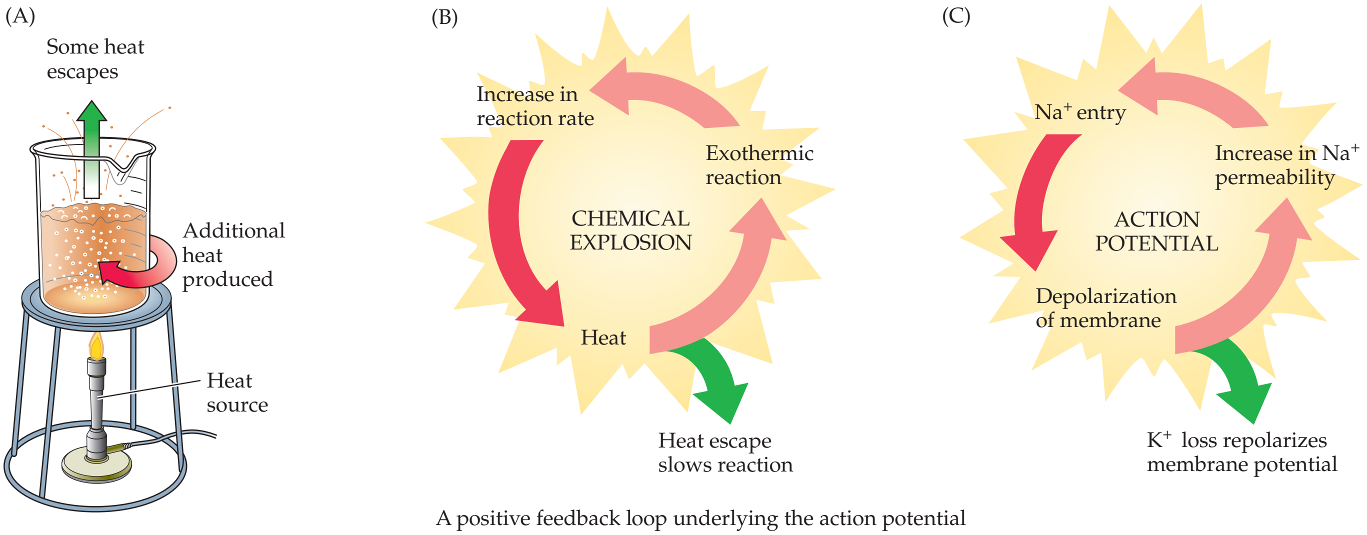
Threshold

An important—and potentially puzzling—property of the action potential is its initiation at a particular membrane potential, called threshold. Indeed, action potentials never occur without a depolarizing stimulus that brings the membrane to this level. The depolarizing "trigger" can be one of several events: a synaptic input, a receptor potential generated by specialized receptor organs, the endogenous pacemaker activity of cells that generate action potentials spontaneously, or the local current that mediates the spread of the action potential down the axon.

Why the action potential "takes off" at a particular level of depolarization can be understood by comparing the underlying events to a chemical explosion (Figure A). Exogenous heat (analogous to the initial depolarization of the membrane potential) stimulates an exothermic chemical reaction, which produces more heat, which further enhances the reaction (Figure B). As a result of this positive feedback loop, the rate of the reaction builds up exponentially—the definition of an explosion. In any such process, however, there is a threshold, that is, a point up to which heat can be supplied without resulting in an explosion. The threshold for the chemical explosion diagrammed here is the point at which the amount of heat supplied exogenously is just equal to the amount of heat that can be dissipated by the circumstances of the reaction (such as escape of heat from the beaker).

The threshold of action potential initiation is, in principle, similar (Figure C). There is a range of "subthreshold" depolarization, within which the rate of increased sodium entry is less than the rate of potassium exit (remember that the membrane at rest is highly permeable to K$^+$, which therefore flows out as the membrane is depolarized). The point at which Na$^+$ inflow just equals K$^+$ outflow represents an unstable equilibrium analogous to the ignition point of an explosive mixture. The behavior of the membrane at threshold reflects this instability: The membrane potential may linger at the threshold level for a variable period before either returning to the resting level or flaring up into a full-blown action potential. In theory at least, if there is a net internal gain of a single Na$^+$ ion, an action potential occurs; conversely, the net loss of a single K$^+$ ion leads to repolarization. A more precise definition of threshold, therefore, is that value of membrane potential, in depolarizing from the resting potential, at which the current carried by Na$^+$ entering the neuron is exactly equal to the K$^+$ current that is flowing out. Once the triggering event depolarizes the membrane beyond this point, the positive feedback loop of Na$^+$ entry on membrane potential closes and the action potential "fires."

Because the Na$^+$ and K$^+$ conductances change dynamically over time, the threshold potential for producing an action potential also varies as a consequence of the previous activity of the neuron. For example, following an action potential, the membrane becomes temporarily refractory to further excitation because the threshold for firing an action potential transiently rises. There is, therefore, no specific value of membrane potential that defines the threshold for a given nerve cell in all circumstances.


(A)
Some heat escapes
Additional heat produced
Heat source
(B)
Increase in reaction rate
Exothermic reaction
CHEMICAL EXPLOSION
Heat
Heat escape slows reaction
(C)
Na$^+$ entry
Increase in Na$^+$ permeability
ACTION POTENTIAL
Depolarization of membrane
K$^+$ loss repolarizes membrane potential

A positive feedback loop underlying the action potential explains the phenomenon of threshold.

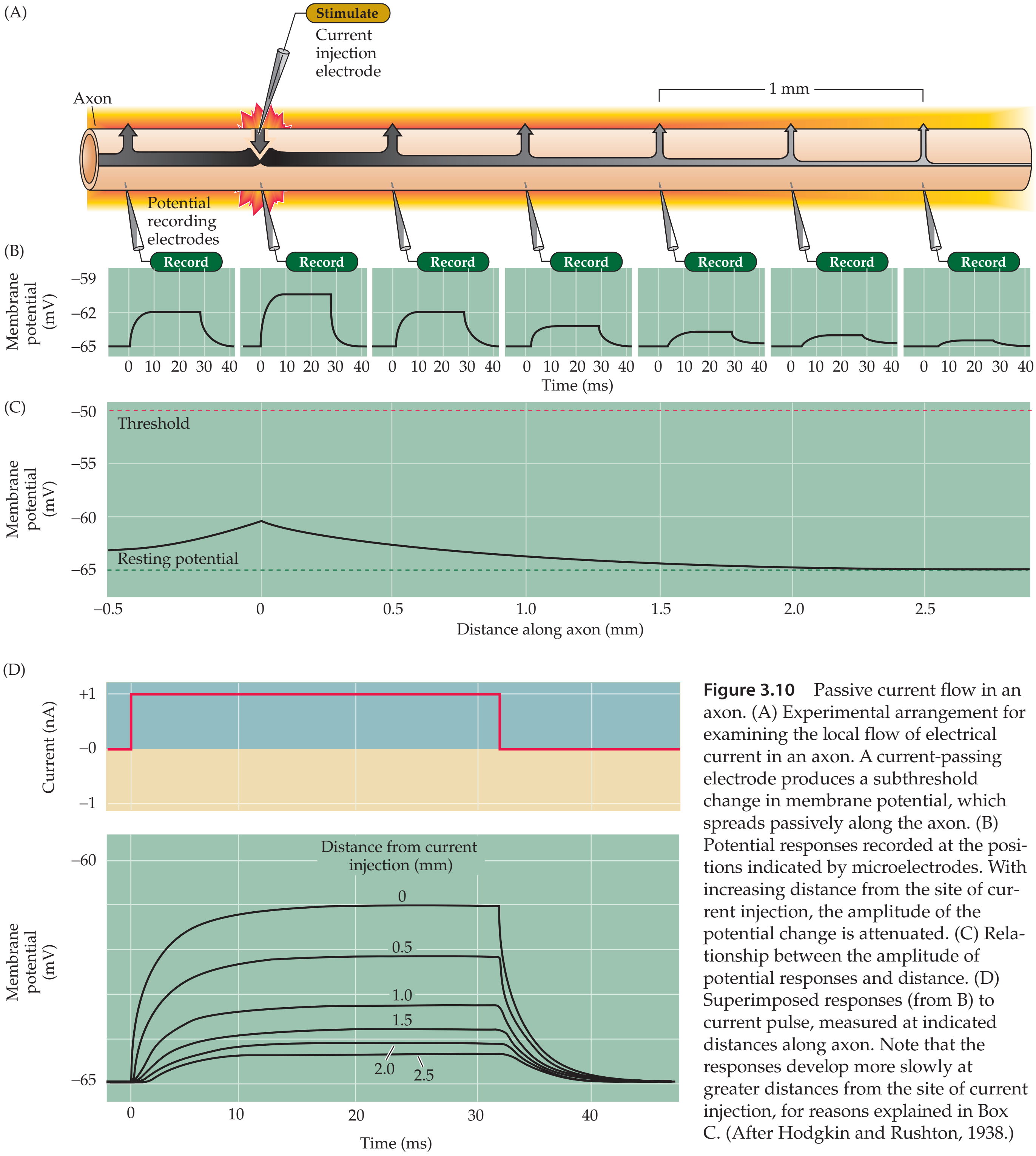


Figure 3.10 Passive current flow in an axon. (A) Experimental arrangement for examining the local flow of electrical current in an axon. A current-passing electrode produces a subthreshold change in membrane potential, which spreads passively along the axon. (B) Potential responses recorded at the positions indicated by microelectrodes. With increasing distance from the site of current injection, the amplitude of the potential change is attenuated. (C) Relationship between the amplitude of potential responses and distance. (D) Superimposed responses (from B) to current pulse, measured at indicated distances along axon. Note that the responses develop more slowly at greater distances from the site of current injection, for reasons explained in Box C. (After Hodgkin and Rushton, 1938.)

If the experiment shown in Figure 3.10 is repeated with a depolarizing current pulse large enough to produce an action potential, the result is dramatically different (Figure 3.11A). In this case, an action potential occurs without decrement along the entire length of the axon, which in humans

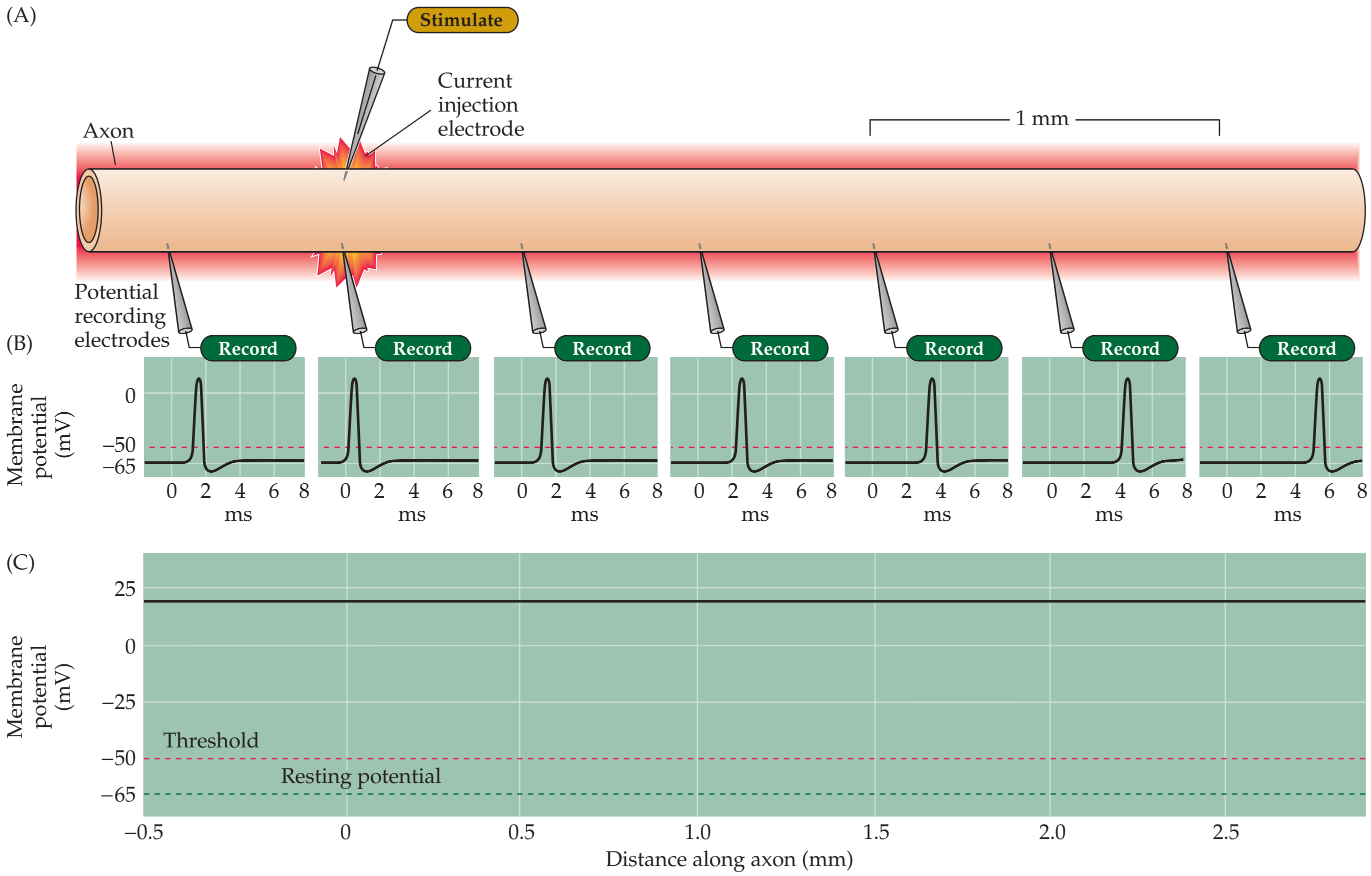


Figure 3.11 Propagation of an action potential. (A) In this experimental arrangement, an electrode evokes an action potential by injecting a suprathreshold current. (B) Potential responses recorded at the positions indicated by microelectrodes. The amplitude of the action potential is constant along the length of the axon, although the time of appearance of the action potential is delayed with increasing distance. (C) The constant amplitude of an action potential (solid black line) measured at different distances.

may be a distance of a meter or more (Figure 3.11B). Thus, action potentials somehow circumvent the inherent leakiness of neurons.

How, then, do action potentials traverse great distances along such a poor passive conductor? The answer is in part provided by the observation that the amplitude of the action potentials recorded at different distances is constant. This all-or-none behavior indicates that more than simple passive flow of current must be involved in action potential propagation. A second clue comes from examination of the time of occurrence of the action potentials recorded at different distances from the site of stimulation: Action potentials occur later and later at greater distances along the axon (Figure 3.11B). Thus, the action potential has a measurable rate of transmission, called the **conduction velocity**. The delay in the arrival of the action potential at successively more distant points along the axon differs from the case shown in Figure 3.10, in which the electrical changes produced by passive current flow occur at more or less the same time at successive points.

The mechanism of action potential propagation is easy to grasp once one understands how action potentials are generated and how current passively flows along an axon (Figure 3.12). A depolarizing stimulus—a synaptic potential or a receptor potential in an intact neuron, or an injected current pulse in an experiment—locally depolarizes the axon, thus opening the voltage-sensitive Na^+ channels in that region. The opening of Na^+ channels causes inward movement of Na^+, and the resultant depolarization of the membrane potential generates an action potential at that site. Some of the local current generated by the action potential will then flow passively down the axon, in the same way that subthreshold currents spread along the axon (see Figure 3.10). Note that this passive current flow does not require the movement of Na^+ along the axon but, instead, occurs by a shuttling of charge, somewhat similar to what happens when wires passively conduct electricity by transmission of electron charge. This passive current flow depolarizes the membrane potential in the adjacent region of the axon, thus opening the Na^+ channels in the neighboring membrane. The local depolarization triggers an action potential in this region, which then spreads again in a continuing cycle until the end of the axon is reached. Thus, action potential propagation requires the coordinated action of two forms of current

Box C
Passive Membrane Properties

The passive flow of electrical current plays a central role in action potential propagation, synaptic transmission, and all other forms of electrical signaling in nerve cells. Therefore, it is worthwhile understanding in quantitative terms how passive current flow varies with distance along a neuron. For the case of a cylindrical axon, such as the one depicted in Figure 3.10, subthreshold current injected into one part of the axon spreads passively along the axon until the current is dissipated by leakage out across the axon membrane. The decrement in the current flow with distance (Figure A) is described by a simple exponential function:

$$V_x = V_0 \, e^{-x/\lambda}$$

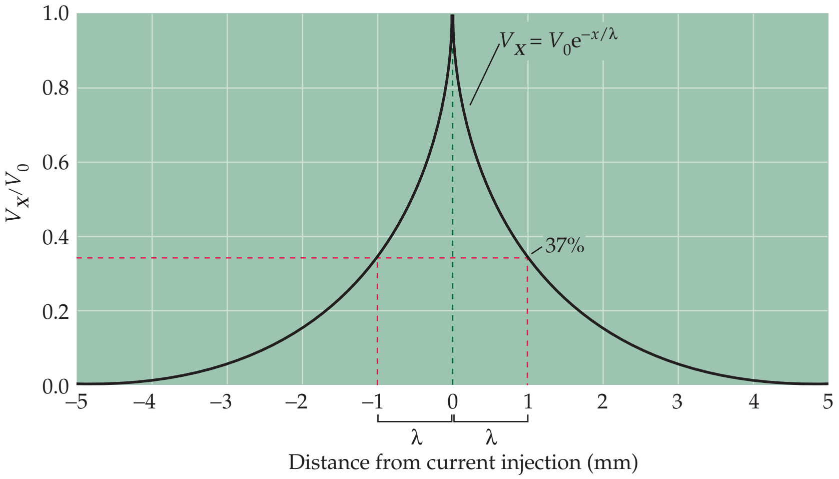
where V_x is the voltage response at any distance x along the axon, V_0 is the voltage change at the point where current is injected into the axon, e is the base of natural logarithms (approximately 2.7), and λ is the length constant of the axon. As evident in this relationship, the length constant is the distance where the initial voltage response (V_0) decays to 1/e (or 37%) of its value. The length constant is thus a way to characterize how far passive current flow spreads before it leaks out of the axon, with leakier axons having shorter length constants.

The length constant depends upon the physical properties of the axon, in particular the relative resistances of the plasma membrane (r_m), the intracellular axoplasm (r_i), and the extracellular medium (r_0). The relationship between these parameters is:

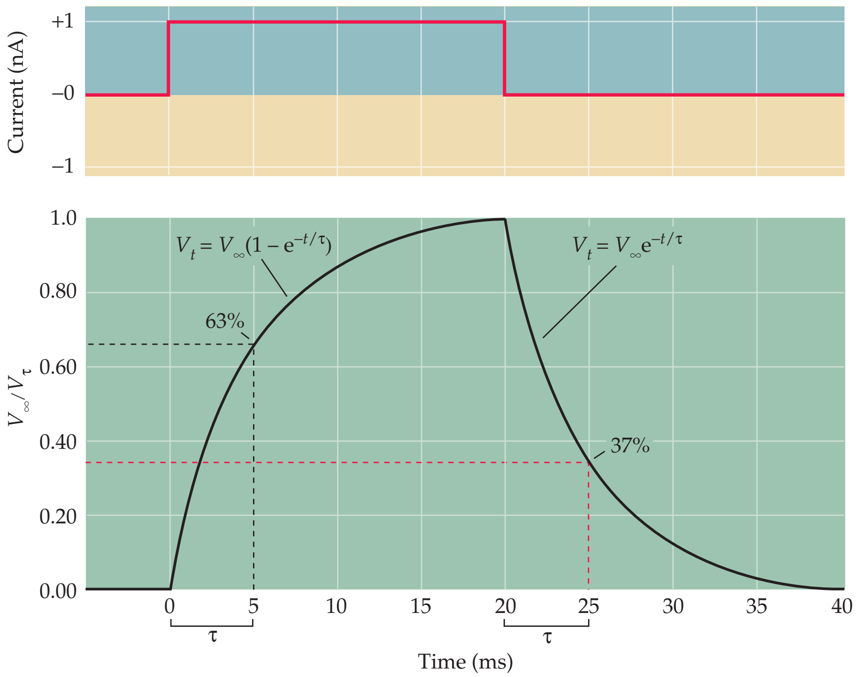
$$\lambda = \sqrt{\frac{r_m}{r_0 + r_i}}$$

Hence, to improve the passive flow of current along an axon, the resistance of the plasma membrane should be as high as possible and the resistances of the axoplasm and extracellular medium should be low.

Another important consequence of the passive properties of neurons is that currents flowing across a membrane do not immediately change the membrane potential. For example, when a rectangular current pulse is injected into the axon shown in the experiment illustrated in Figure 3.10A, the membrane potential depolarizes slowly over a few milliseconds and then repolarizes over a similar time course when the current pulse ends (see Figure 3.10D). These delays in changing the membrane potential are due to the fact that the plasma mem-



(A) Spatial decay of membrane potential along a cylindrical axon. A current pulse injected at one point in the axon (0 mm) produces voltage responses (V_x) that decay exponentially with distance. The distance where the voltage response is 1/e of its initial value (V_0) is the length constant, λ.



(B) Time course of potential changes produced in a spatially uniform cell by a current pulse. The rise and fall of the membrane potential (V_t) can be described as exponential functions, with the time constant τ defining the time required for the response to rise to 1 – (1/e) of the steady-state value (V_∞), or to decline to 1/e of V_∞.

brane behaves as a capacitor, storing the initial charge that flows at the beginning and end of the current pulse. For the case of a cell whose membrane potential is spatially uniform, the change in the membrane potential at any time, V_t, after beginning the current pulse (Figure B) can also be described by an exponential relationship:

$$V_t = V_\infty(1 - e^{-t/\tau})$$

where V_∞ is the steady-state value of the membrane potential change, t is the time after the current pulse begins, and τ is the membrane time constant. The time constant is thus defined as the time when the voltage response (V_t) rises to 1 – (1/e) (or 63%) of V_∞. After the current pulse ends, the membrane potential change also declines exponentially according to the relationship

$$V_t = V_\infty e^{-t/\tau}$$

During this decay, the membrane potential returns to 1/e of V_∞ at a time equal to t. For cells with more complex geometries than the axon in Figure 3.10, the time courses of the changes in membrane potential are not simple exponentials, but nonetheless depend on the membrane time constant. Thus, the time constant characterizes how rapidly current flow changes the membrane potential. The membrane time constant also depends on the physical properties of the nerve cell, specifically on the resistance (r_m) and capacitance (c_m) of the plasma membrane such that:

$$\tau = r_m c_m$$

The values of r_m and c_m depend, in part, on the size of the neuron, with larger cells having lower resistances and larger capacitances. In general, small nerve cells tend to have long time constants and large cells brief time constants.

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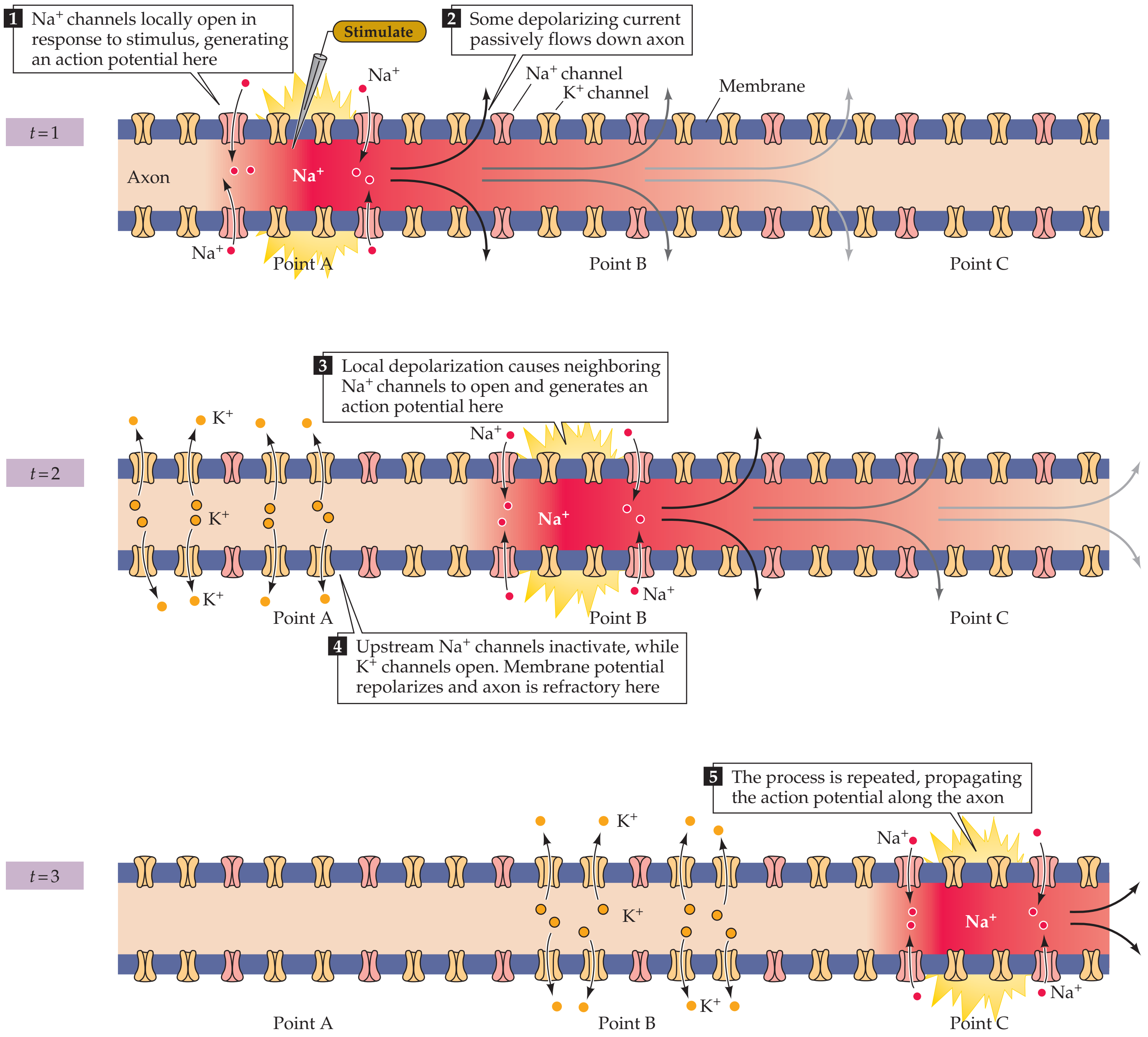
flow—the passive flow of current as well as active currents flowing through voltage-dependent ion channels. The regenerative properties of Na^+ channel opening allow action potentials to propagate in an all-or-none fashion by acting as a booster at each point along the axon, thus ensuring the long-distance transmission of electrical signals.

The Refractory Period

Recall that the depolarization that produces Na^+ channel opening also causes delayed activation of K^+ channels and Na^+ channel inactivation, lead-


1 Na+ channels locally open in response to stimulus, generating an action potential here
Stimulate
2 Some depolarizing current passively flows down axon
Na+
Na+ channel
K+ channel
Membrane
t=1
Axon
Na+
Na+
Point A
Point B
Point C
3 Local depolarization causes neighboring Na+ channels to open and generates an action potential here
K+
Na+
t=2
K+
Na+
Na+
K+
Point A
Point B
Point C
4 Upstream Na+ channels inactivate, while K+ channels open. Membrane potential repolarizes and axon is refractory here
5 The process is repeated, propagating the action potential along the axon
K+
Na+
t=3
K+
Na+
Na+
K+
Point A
Point B
Point C

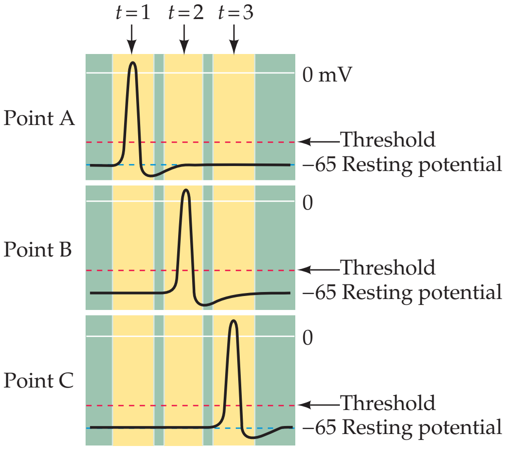


Figure 3.12 Action potential conduction requires both active and passive current flow. Depolarization opens Na$^+$ channels locally and produces an action potential at point A of the axon (time $t = 1$). The resulting inward current flows passively along the axon, depolarizing the adjacent region (point B) of the axon. At a later time ($t = 2$), the depolarization of the adjacent membrane has opened Na$^+$ channels at point B, resulting in the initiation of the action potential at this site and additional inward current that again spreads passively to an adjacent point (point C) farther along the axon. At a still later time ($t = 3$), the action potential has propagated even farther. This cycle continues along the full length of the axon. Note that as the action potential spreads, the membrane potential repolarizes due to K$^+$ channel opening and Na$^+$ channel inactivation, leaving a "wake" of refractoriness behind the action potential that prevents its backward propagation (panel 4). The panel to the left of this figure legend shows the time course of membrane potential changes at the points indicated.

ing to repolarization of the membrane potential as the action potential sweeps along the length of an axon (see Figure 3.12). In its wake, the action potential leaves the Na^+ channels inactivated and K^+ channels activated for a brief time. These transitory changes make it harder for the axon to produce subsequent action potentials during this interval, which is called the **refractory period**. Thus, the refractory period limits the number of action potentials that a given nerve cell can produce per unit time. As might be expected, different types of neurons have different maximum rates of action potential firing due to different types and densities of ion channels. The refractoriness of the membrane in the wake of the action potential also explains why action potentials do not propagate back toward the point of their initiation as they travel along an axon.

Increased Conduction Velocity as a Result of Myelination

The rate of action potential conduction limits the flow of information within the nervous system. It is not surprising, then, that various mechanisms have evolved to optimize the propagation of action potentials along axons. Because action potential conduction requires passive and active flow of current (see Figure 3.12), the rate of action potential propagation is determined by both of these phenomena. One way of improving passive current flow is to increase the diameter of an axon, which effectively decreases the internal resistance to passive current flow (see Box C). The consequent increase in action potential conduction velocity presumably explains why giant axons evolved in invertebrates such as squid, and why rapidly conducting axons in all animals tend to be larger than slowly conducting ones.

Another strategy to improve the passive flow of electrical current is to insulate the axonal membrane, reducing the ability of current to leak out of the axon and thus increasing the distance along the axon that a given local current can flow passively (see Box C). This strategy is evident in the **myelination** of axons, a process by which oligodendrocytes in the central nervous system (and Schwann cells in the peripheral nervous system) wrap the axon in **myelin**, which consists of multiple layers of closely opposed glial membranes (Figure 3.13; see also Chapter 1). By acting as an electrical insulator, myelin greatly speeds up action potential conduction (Figure 3.14). For example, whereas unmyelinated axon conduction velocities range from about 0.5 to 10 m/s, myelinated axons can conduct at velocities of up to 150 m/s. The major reason underlying this marked increase in speed is that the time-consuming process of action potential generation occurs only at specific points along the axon, called **nodes of Ranvier**, where there is a gap in the myelin wrapping (see Figure 1.4F). If the entire surface of an axon were insulated, there would be no place for current to flow out of the axon and action potentials could not be generated. As it happens, an action potential generated at one node of Ranvier elicits current that flows passively within the myelinated segment until the next node is reached. This local current flow then generates an action potential in the neighboring segment, and the cycle is repeated along the length of the axon. Because current flows across the neuronal membrane only at the nodes (see Figure 3.13), this type of propagation is called **saltatory**, meaning that the action potential jumps from node to node. Not surprisingly, loss of myelin, as occurs in diseases such as multiple sclerosis, causes a variety of serious neurological problems (Box D).

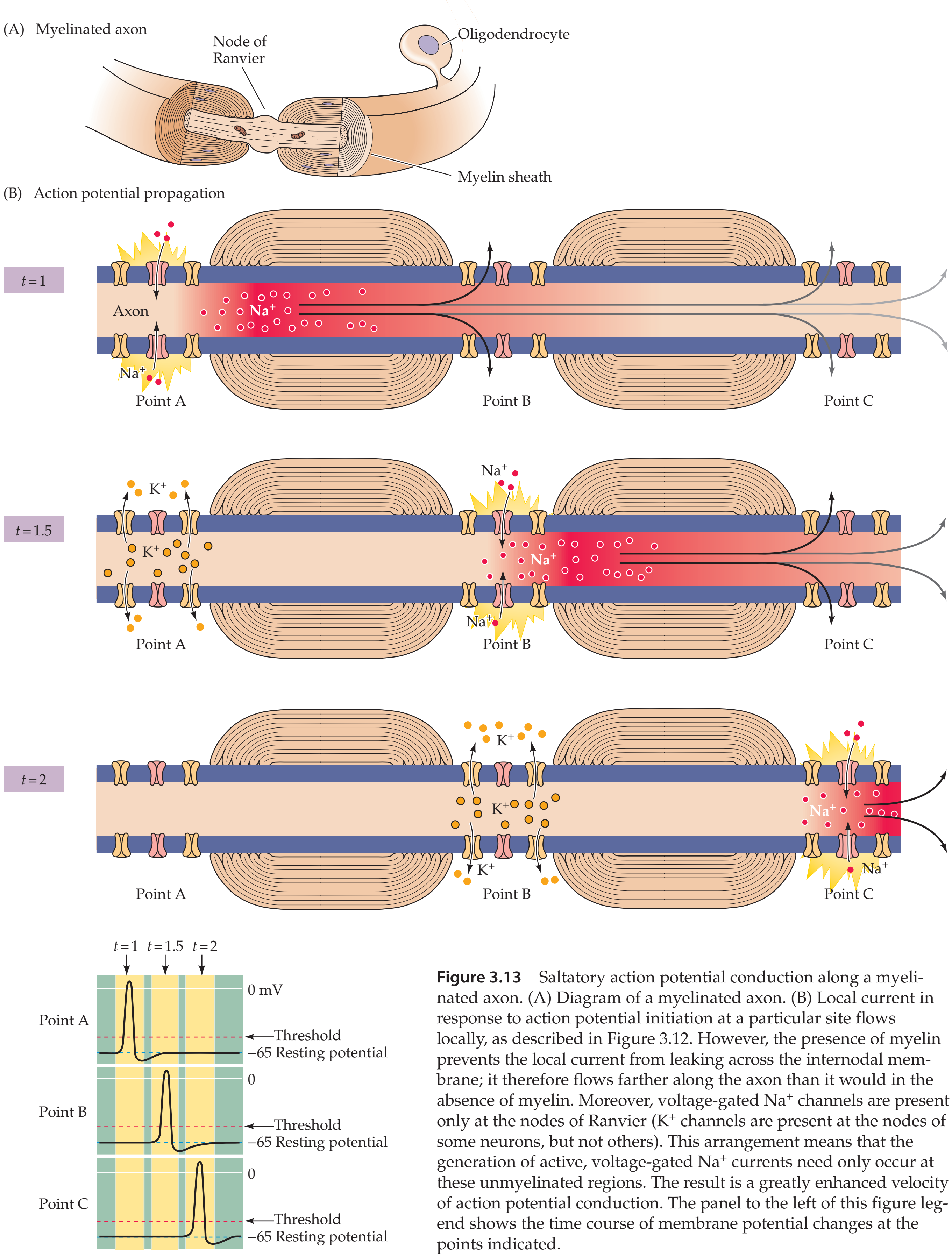

(A) Myelinated axon
Node of Ranvier
Oligodendrocyte
Myelin sheath
(B) Action potential propagation
t=1
Axon
Na+
Na+
Point A
Point B
Point C
t=1.5
K+
K+
Na+
Na+
Na+
Point A
Point B
Point C
t=2
K+
K+
K+
Na+
Na+
Point A
Point B
Point C
t=1
t=1.5
t=2
Point A
0 mV
Threshold
−65 Resting potential
Point B
0
Threshold
−65 Resting potential
Point C
0
Threshold
−65 Resting potential

Figure 3.13 Saltatory action potential conduction along a myelinated axon. (A) Diagram of a myelinated axon. (B) Local current in response to action potential initiation at a particular site flows locally, as described in Figure 3.12. However, the presence of myelin prevents the local current from leaking across the internodal membrane; it therefore flows farther along the axon than it would in the absence of myelin. Moreover, voltage-gated Na^+ channels are present only at the nodes of Ranvier (K^+ channels are present at the nodes of some neurons, but not others). This arrangement means that the generation of active, voltage-gated Na^+ currents need only occur at these unmyelinated regions. The result is a greatly enhanced velocity of action potential conduction. The panel to the left of this figure legend shows the time course of membrane potential changes at the points indicated.

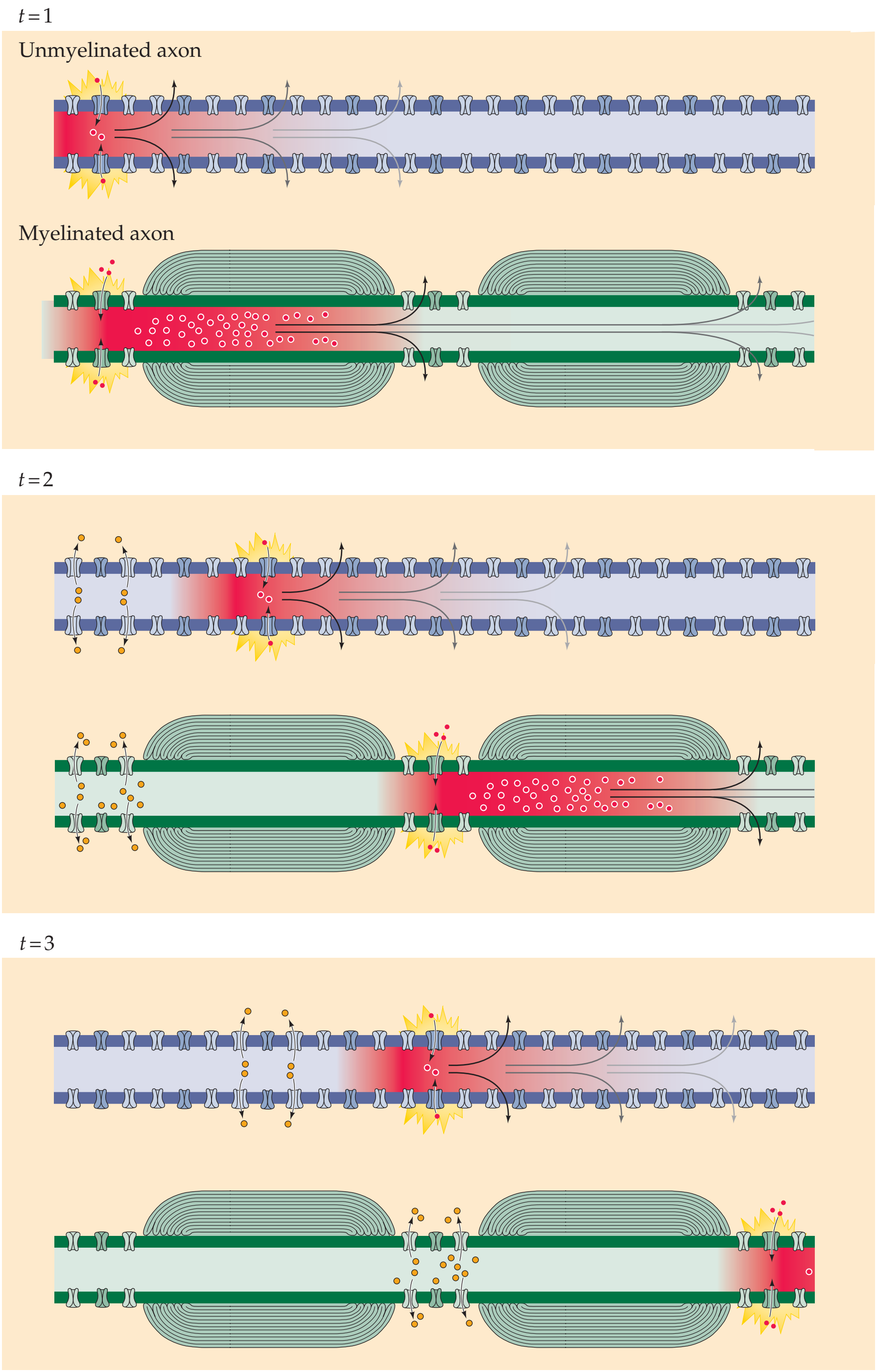


Figure 3.14 Comparison of speed of action potential conduction in unmyelinated (upper) and myelinated (lower) axons.

Summary

The action potential and all its complex properties can be explained by time- and voltage-dependent changes in the Na^+ and K^+ permeabilities of neuronal membranes. This conclusion derives primarily from evidence obtained by a device called the voltage clamp. The voltage clamp technique is an electronic feedback method that allows control of neuronal membrane potential

Box D

Multiple Sclerosis

Multiple sclerosis (MS) is a disease of the central nervous system characterized by a variety of clinical problems arising from multiple regions of demyelination and inflammation along axonal pathways. The disorder commonly begins between ages 20 and 40, characterized by the abrupt onset of neurological deficits that typically persist for days or weeks and then remit. The clinical course ranges from patients with no persistent neurological loss, some of whom experience only occasional later exacerbations, to others who progressively deteriorate as a result of extensive and relentless central nervous system involvement.

The signs and symptoms of MS are determined by the location of the affected regions. Particularly common are monocular blindness (due to lesions of the optic nerve), motor weakness or paralysis (due to lesions of the corticospinal tracts), abnormal somatic sensations (due to lesions of somatic sensory pathways, often in the posterior columns), double vision (due to lesions of medial longitudinal fasciculus), and dizziness (due to lesions of vestibular pathways). Abnormalities are often apparent in the cerebrospinal fluid, which usually contains an abnormal number of cells associated with inflammation and an increased content of antibodies (a sign of an altered immune response). The diagnosis of MS generally relies on the presence of a neurological problem that remits and then returns at an unrelated site. Confirmation can sometimes be obtained from magnetic resonance imaging (MRI), or functional evidence of lesions in a particular pathway by abnormal evoked potentials. The histological hallmark of MS at postmortem exam is multiple lesions at different sites showing loss of myelin associated with infiltration of inflammatory cells and, in some instances, loss of axons themselves.

The concept of MS as a demyelinating disease is deeply embedded in the clinical literature, although precisely how the demyelination translates into functional deficits is poorly understood. The loss of the myelin sheath surrounding many axons clearly compromises action potential conduction, and the abnormal patterns of nerve conduction that result presumably produce most of the clinical deficits in the disease. However, MS may have effects that extend beyond loss of the myelin sheath. It is clear that some axons are actually destroyed, probably as a result of inflammatory processes in the overlying myelin and/or loss of trophic support of the axon by oligodendrocytes. Thus, axon loss also contributes to the functional deficits in MS, especially in the chronic, progressive forms of the disease.

The ultimate cause of MS remains unclear. The immune system undoubtedly contributes to the damage and new immunoregulatory therapies provide substantial benefits to many patients. Precisely how the immune system is activated to cause the injury is not known. The most popular hypothesis is that MS is an autoimmune disease (i.e., a disease in which the immune system attacks the body's proper constituents). The fact that immunization of experimental animals with any one of several molecular constituents of the myelin sheath can induce a demyelinating disease (called experimental allergic encephalomyelitis) shows that an autoimmune attack on the myelin membrane is sufficient to produce a picture similar to MS. A possible explanation of the human disease is that a genetically susceptible individual becomes transiently infected (by a minor viral illness, for example) with a microorganism that expresses a molecule structurally similar to a component of myelin. An immune response to this antigen is mounted to attack the invader, but the failure of the immune system to discriminate between the foreign protein and self results in destruction of otherwise normal myelin, a scenario occurring in mice infected with Theiler's virus.

An alternative hypothesis is that MS is caused by a persistent infection by a virus or other microorganism. In this interpretation, the immune system's ongoing efforts to get rid of the pathogen cause the damage to myelin. Tropical spastic paraparesis (TSP) provides a precedent for this idea. TSP is a disease characterized by the gradual progression of weakness of the legs and impaired control of bladder function associated with increased deep tendon reflexes and a positive Babinski sign (see Chapter 16). This clinical picture is similar to that of rapidly advancing MS. TSP is known to be caused by persistent infection with a retrovirus (human T lymphotropic virus-1). This precedent notwithstanding, proving the persistent viral infection hypothesis for MS requires unambiguous demonstration of the presence of a virus. Despite periodic reports of a virus associated with MS, convincing evidence has not been forthcoming. In sum, MS remains a daunting clinical challenge.

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and, simultaneously, direct measurement of the voltage-dependent fluxes of Na^+ and K^+ that produce the action potential. Voltage clamp experiments show that a transient rise in Na^+ conductance activates rapidly and then inactivates during a sustained depolarization of the membrane potential. Such experiments also demonstrate a rise in K^+ conductance that activates in a delayed fashion and, in contrast to the Na^+ conductance, does not inactivate. Mathematical modeling of the properties of these conductances indicates that they, and they alone, are responsible for the production of all-or-none action potentials in the squid axon. Action potentials propagate along the nerve cell axons initiated by the voltage gradient between the active and inactive regions of the axon by virtue of the local current flow. In this way, action potentials compensate for the relatively poor passive electrical properties of nerve cells and enable neural signaling over long distances. These classical electrophysiological findings provide a solid basis for considering the functional and ultimately molecular variations on neural signaling taken up in the next chapter.

Additional Reading

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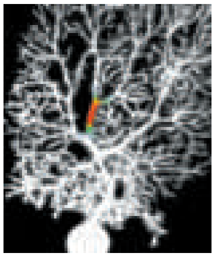
Chapter 4



Channels and Transporters

Overview

The generation of electrical signals in neurons requires that plasma membranes establish concentration gradients for specific ions and that these membranes undergo rapid and selective changes in the membrane permeability to these ions. The membrane proteins that create and maintain ion gradients are called active transporters, whereas other proteins called ion channels give rise to selective ion permeability changes. As their name implies, ion channels are transmembrane proteins that contain a specialized structure, called a pore, that permits particular ions to cross the neuronal membrane. Some of these channels also contain other structures that are able to sense the electrical potential across the membrane. Such voltage-gated channels open or close in response to the magnitude of the membrane potential, allowing the membrane permeability to be regulated by changes in this potential. Other types of ion channels are gated by extracellular chemical signals such as neurotransmitters, and some by intracellular signals such as second messengers. Still others respond to mechanical stimuli, temperature changes, or a combination of such effects. Many types of ion channels have now been characterized at both the gene and protein level, resulting in the identification of a large number of ion channel subtypes that are expressed differentially in neuronal and non-neuronal cells. The specific expression pattern of ion channels in each cell type can generate a wide spectrum of electrical characteristics. In contrast to ion channels, active transporters are membrane proteins that produce and maintain ion concentration gradients. The most important of these is the Na^+ pump, which hydrolyzes ATP to regulate the intracellular concentrations of both Na^+ and K^+. Other active transporters produce concentration gradients for the full range of physiologically important ions, including Cl^-, Ca^{2+}, and H^+. From the perspective of electrical signaling, active transporters and ion channels are complementary: Transporters create the concentration gradients that help drive ion fluxes through open ion channels, thus generating electrical signals.

Ion Channels Underlying Action Potentials

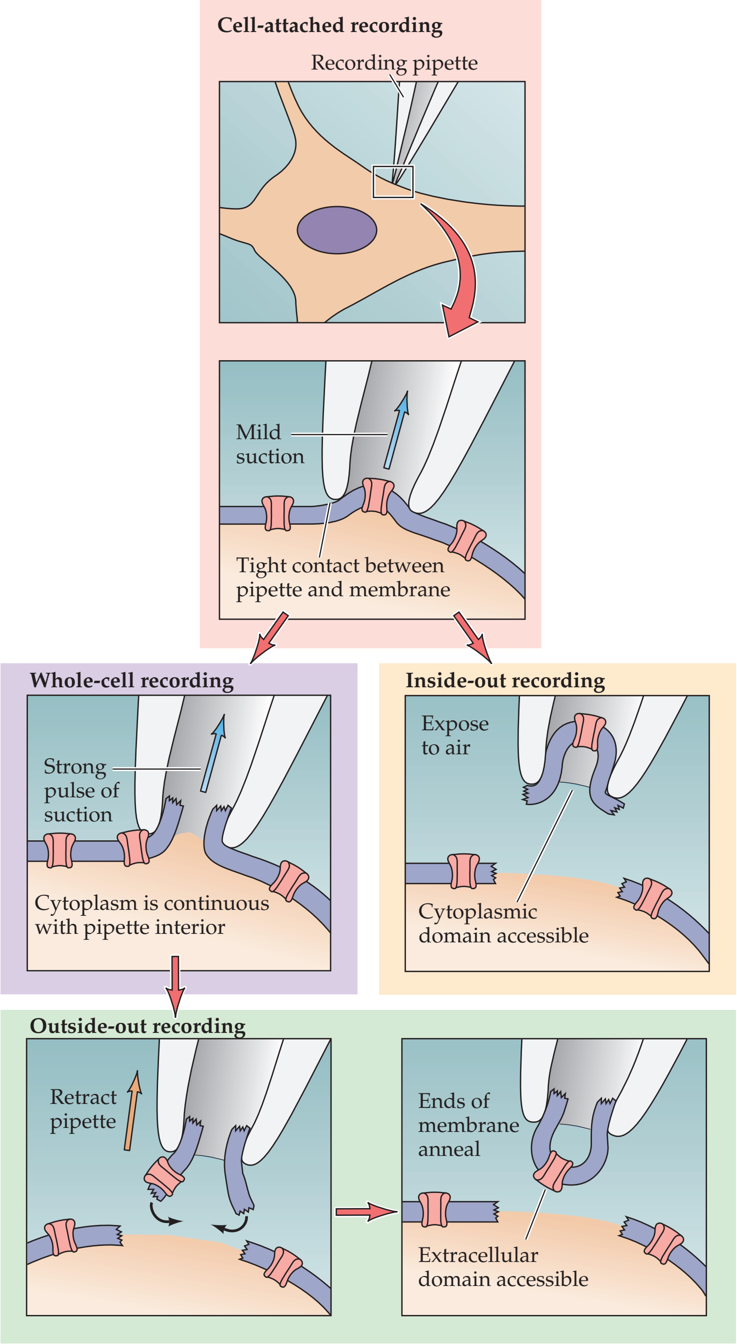
Although Hodgkin and Huxley had no knowledge of the physical nature of the conductance mechanisms underlying action potentials, they nonetheless proposed that nerve cell membranes have channels that allow ions to pass selectively from one side of the membrane to the other (see Chapter 3). Based on the ionic conductances and currents measured in voltage clamp experiments, the postulated channels had to have several properties. First, because the ionic currents are quite large, the channels had to be capable of allowing ions to move across the membrane at high rates. Second, because

Box A

The Patch Clamp Method

A wealth of new information about ion channels resulted from the invention of the patch clamp method in the 1970s. This technique is based on a very simple idea. A glass pipette with a very small opening is used to make tight contact with a tiny area, or patch, of neuronal membrane. After the application of a small amount of suction to the back of the pipette, the seal between pipette and membrane becomes so tight that no ions can flow between the pipette and the membrane. Thus, all the ions that flow when a single ion channel opens must flow into the pipette. The resulting electrical current, though small, can be measured with an ultrasensitive electronic amplifier connected to the pipette. Based on the geometry involved, this arrangement usually is called the *cell-attached patch clamp recording method*. As with the conventional voltage clamp method, the patch clamp method allows experimental control of the membrane potential to characterize the voltage dependence of membrane currents.

Although the ability to record currents flowing through single ion channels is an important advantage of the cell-attached patch clamp method, minor technical modifications yield still other advantages. For example, if the membrane patch within the pipette is disrupted by briefly applying strong suction, the interior of the pipette becomes continuous with the cytoplasm of the cell. This arrangement allows measurements of electrical potentials and currents from the entire cell and is therefore called the *whole-cell recording method*. The whole-cell configuration also allows diffusional exchange between the pipette and the cytoplasm, producing a convenient way to inject substances into the interior of a "patched" cell.


Cell-attached recording
Recording pipette
Mild suction
Tight contact between pipette and membrane
Whole-cell recording
Strong pulse of suction
Cytoplasm is continuous with pipette interior
Inside-out recording
Expose to air
Cytoplasmic domain accessible
Outside-out recording
Retract pipette
Ends of membrane anneal
Extracellular domain accessible

Four configurations in patch clamp measurements of ionic currents.

Two other variants of the patch clamp method originate from the finding that once a tight seal has formed between the membrane and the glass pipette, small pieces of membrane can be pulled away from the cell without disrupting the seal; this yields a preparation that is free of the complications imposed by the rest of the cell. Simply retracting a pipette that is in the cell-attached configuration causes a small vesicle of membrane to remain attached to the pipette. By exposing the tip of the pipette to air, the vesicle opens to yield a small patch of membrane with its (former) intracellular surface exposed. This arrangement, called the inside-out patch recording configuration, allows the measurement of single-channel currents with the added benefit of making it possible to change the medium to which the intracellular surface of the membrane is exposed. Thus, the inside-out configuration is particularly valuable when studying the influence of intracellular molecules on ion channel function. Alternatively, if the pipette is retracted while it is in the whole-cell configuration, a membrane patch is produced that has its extracellular surface exposed. This arrangement, called the outside-out recording configuration, is optimal for studying how channel activity is influenced by extracellular chemical signals, such as neurotransmitters (see Chapter 5). This range of possible configurations makes the patch clamp method an unusually versatile technique for studies of ion channel function.

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the ionic currents depend on the electrochemical gradient across the membrane, the channels had to make use of these gradients. Third, because Na^+ and K^+ flow across the membrane independently of each other, different channel types had to be capable of discriminating between Na^+ and K^+, allowing only one of these ions to flow across the membrane under the relevant conditions. Finally, given that the conductances are voltage-dependent, the channels had to be able to sense the voltage drop across the membrane, opening only when the voltage reached appropriate levels. While this concept of channels was highly speculative in the 1950s, later experimental work established beyond any doubt that transmembrane proteins called voltage-sensitive ion channels indeed exist and are responsible for all of the ionic conductance phenomena described in Chapter 3.

The first direct evidence for the presence of voltage-sensitive, ion-selective channels in nerve cell membranes came from measurements of the ionic currents flowing through individual ion channels. The voltage-clamp apparatus used by Hodgkin and Huxley could only resolve the *aggregate* current resulting from the flow of ions through many thousands of channels. A technique capable of measuring the currents flowing through single channels was devised in 1976 by Erwin Neher and Bert Sakmann at the Max Planck Institute in Goettingen. This remarkable approach, called patch clamping (Box A), revolutionized the study of membrane currents. In particular, the patch clamp method provided the means to test directly Hodgkin and Huxley's proposals about the characteristics of ion channels.

Currents flowing through Na^+ channels are best examined in experimental circumstances that prevent the flow of current through other types of channels that are present in the membrane (e.g., K^+ channels). Under such conditions, depolarizing a patch of membrane from a squid giant axon causes tiny inward currents to flow, but only occasionally (Figure 4.1). The size of these currents is minuscule—approximately l–2 pA (i.e., 10^{-12} ampere), which is orders of magnitude smaller than the Na^+ currents measured by voltage clamping the entire axon. The currents flowing through single channels are called **microscopic currents** to distinguish them from the **macroscopic currents** flowing through a large number of channels distributed over a much more extensive region of surface membrane. Although microscopic currents are certainly small, a current of 1 pA nonetheless reflects the flow of thousands of ions per millisecond. Thus, as predicted, a single channel can let many ions pass through the membrane in a very short time.

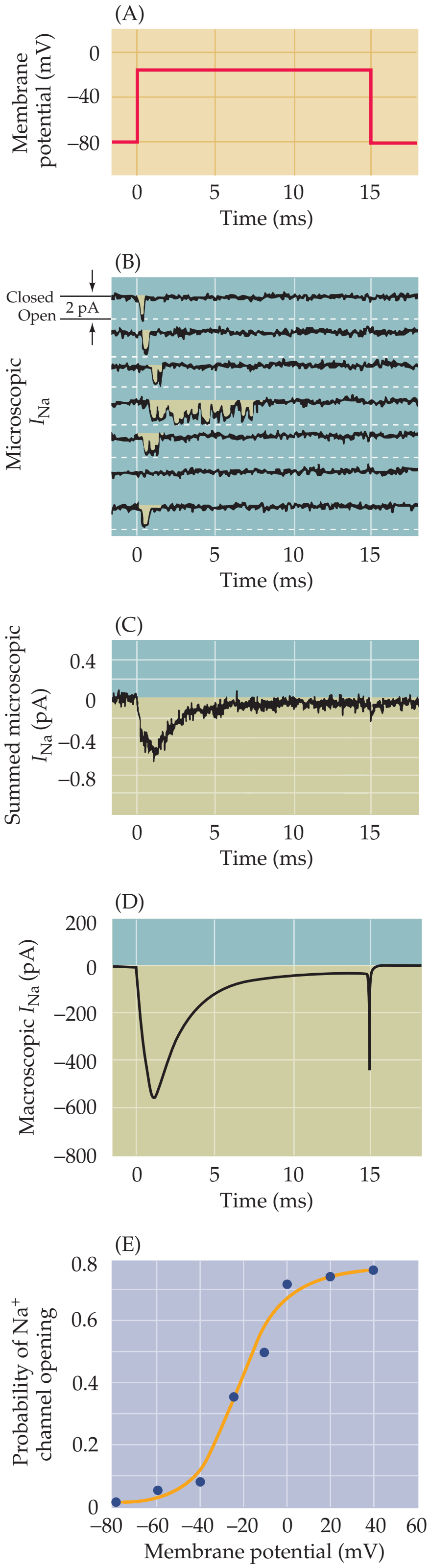

Figure 4.1 Patch clamp measurements of ionic currents flowing through single Na^+ channels in a squid giant axon. In these experiments, Cs^+ was applied to the axon to block voltage-gated K^+ channels. Depolarizing voltage pulses (A) applied to a patch of membrane containing a single Na^+ channel result in brief currents (B, downward deflections) in the seven successive recordings of membrane current (I_{Na}). (C) The sum of many such current records shows that most channels open in the initial 1–2 ms following depolarization of the membrane, after which the probability of channel openings diminishes because of channel inactivation. (D) A macroscopic current measured from another axon shows the close correlation between the time courses of microscopic and macroscopic Na^+ currents. (E) The probability of an Na^+ channel opening depends on the membrane potential, increasing as the membrane is depolarized. (B,C after Bezanilla and Correa, 1995; D after Vandenburg and Bezanilla, 1991; E after Correa and Bezanilla, 1994.)

Several observations further proved that the microscopic currents in Figure 4.1B are due to the opening of single, voltage-activated Na^+ channels. First, the currents are carried by Na^+; thus, they are directed inward when the membrane potential is more negative than E_{Na}, reverse their polarity at E_{Na}, are outward at more positive potentials, and are reduced in size when the Na^+ concentration of the external medium is decreased. This behavior exactly parallels that of the macroscopic Na^+ currents described in Chapter 3. Second, the channels have a time course of opening, closing, and inactivating that matches the kinetics of macroscopic Na^+ currents. This correspondence is difficult to appreciate in the measurement of microscopic currents flowing through a single open channel, because individual channels open and close in a stochastic (random) manner, as can be seen by examining the individual traces in Figure 4.1B. However, repeated depolarization of the membrane potential causes each Na^+ channel to open and close many times. When the current responses to a large number of such stimuli are averaged together, the collective response has a time course that looks much like the macroscopic Na^+ current (Figure 4.1C). In particular, the channels open mostly at the beginning of a prolonged depolarization, showing that they subsequently inactivate, as predicted from the macroscopic Na^+ current (compare Figures 4.1C and 4.1D). Third, both the opening and closing of the channels are voltage-dependent; thus, the channels are closed at –80 mV but open when the membrane potential is depolarized. In fact, the probability that any given channel will be open varies with membrane potential (Figure 4.1E), again as predicted from the macroscopic Na^+ conductance (see Figure 3.7). Finally, tetrodotoxin, which blocks the macroscopic Na^+ current (see Box C), also blocks microscopic Na^+ currents. Taken together, these results show that the macroscopic Na^+ current measured by Hodgkin and Huxley does indeed arise from the aggregate effect of many thousands of microscopic Na^+ currents, each representing the opening of a single voltage-sensitive Na^+ channel.

Patch clamp experiments have also revealed the properties of the channels responsible for the macroscopic K^+ currents associated with action potentials. When the membrane potential is depolarized (Figure 4.2A), microscopic outward currents (Figure 4.2B) can be observed under conditions that block Na^+ channels. The microscopic outward currents exhibit all the features expected for currents flowing through action-potential-related K^+ channels. Thus, the microscopic currents (Figure 4.2C), like their macroscopic counterparts (Figure 4.2D), fail to inactivate during brief depolarizations. Moreover, these single-channel currents are sensitive to ionic manipu-

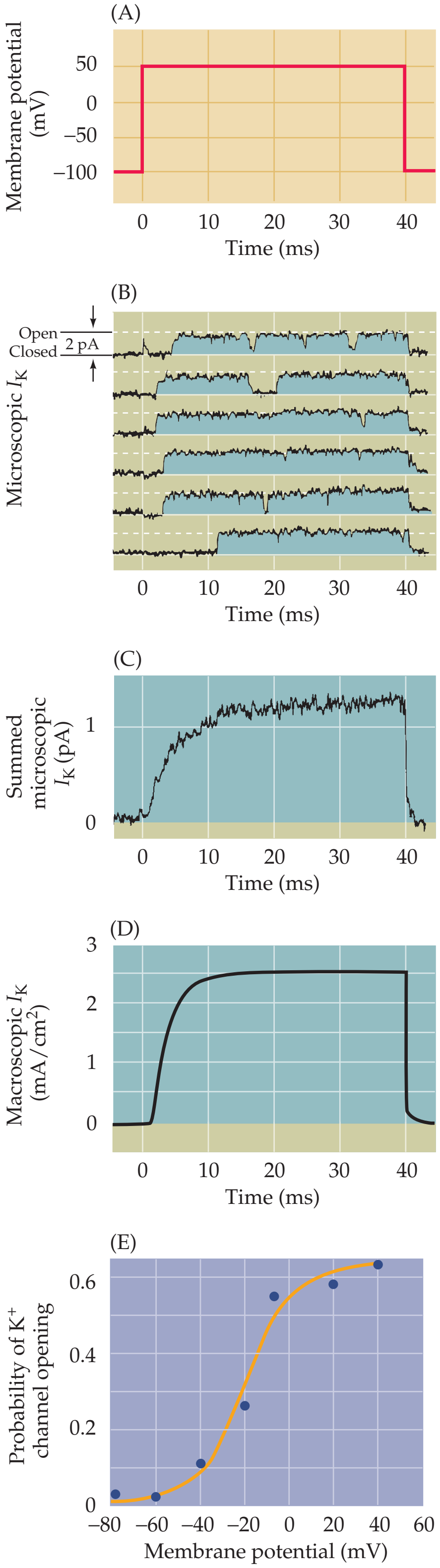

Figure 4.2 Patch clamp measurements of ionic currents flowing through single K$^+$ channels in a squid giant axon. In these experiments, tetrodotoxin was applied to the axon to block voltage-gated Na$^+$ channels. Depolarizing voltage pulses (A) applied to a patch of membrane containing a single K$^+$ channel results in brief currents (B, upward deflections) whenever the channel opens. (C) The sum of such current records shows that most channels open with a delay, but remain open for the duration of the depolarization. (D) A macroscopic current measured from another axon shows the correlation between the time courses of microscopic and macroscopic K$^+$ currents. (E) The probability of a K$^+$ channel opening depends on the membrane potential, increasing as the membrane is depolarized. (B and C after Augustine and Bezanilla, in Hille 1992; D after Augustine and Bezanilla, 1990; E after Perozo et al., 1991.)

lations and drugs that affect the macroscopic K$^+$ currents and, like the macroscopic K$^+$ currents, are voltage-dependent (Figure 4.2E). This and other evidence shows that macroscopic K$^+$ currents associated with action potentials arise from the opening of many voltage-sensitive K$^+$ channels.

In summary, patch clamping has allowed direct observation of microscopic ionic currents flowing through single ion channels, confirming that voltage sensitive Na$^+$ and K$^+$ channels are responsible for the macroscopic conductances and currents that underlie the action potential. Measurements of the behavior of single ion channels has also provided some insight into the molecular attributes of these channels. For example, single channel studies show that the membrane of the squid axon contains at least two types of channels—one selectively permeable to Na$^+$ and a second selectively permeable to K$^+$. Both channel types are **voltage-gated**, meaning that their opening is influenced by membrane potential (Figure 4.3). For each channel, depolarization increases the probability of channel opening, whereas hyperpolarization closes them (see Figures 4.1E and 4.2E). Thus, both channel types must have a **voltage sensor** that detects the potential across the membrane (Figure 4.3). However, these channels differ in important respects. In addition to their different ion selectivities, depolarization also inactivates the Na$^+$ channel but not the K$^+$ channel, causing Na$^+$ channels to pass into a nonconducting state. The Na$^+$ channel must therefore have an additional molecular mechanism responsible for **inactivation**. And, as expected from the macroscopic behavior of the Na$^+$ and K$^+$ currents described in Chapter 3, the kinetic properties of the gating of the two channels differs. This information about the physiology of single channels set the stage for subsequent studies of the molecular diversity of ion channels in various cell types, and of their detailed functional characteristics.

The Diversity of Ion Channels

Molecular genetic studies, in conjunction with the patch clamp method and other techniques, have led to many additional advances in understanding ion channels. Genes encoding Na$^+$ and K$^+$ channels, as well as many other channel types, have now been identified and cloned. A surprising fact that has emerged from these molecular studies is the diversity of genes that code for ion channels. Well over 100 ion channel genes have now been discovered, a number that could not have been anticipated from early studies of ion channel function. To understand the functional significance of this multitude of ion channel genes, the channels can be selectively expressed in well-

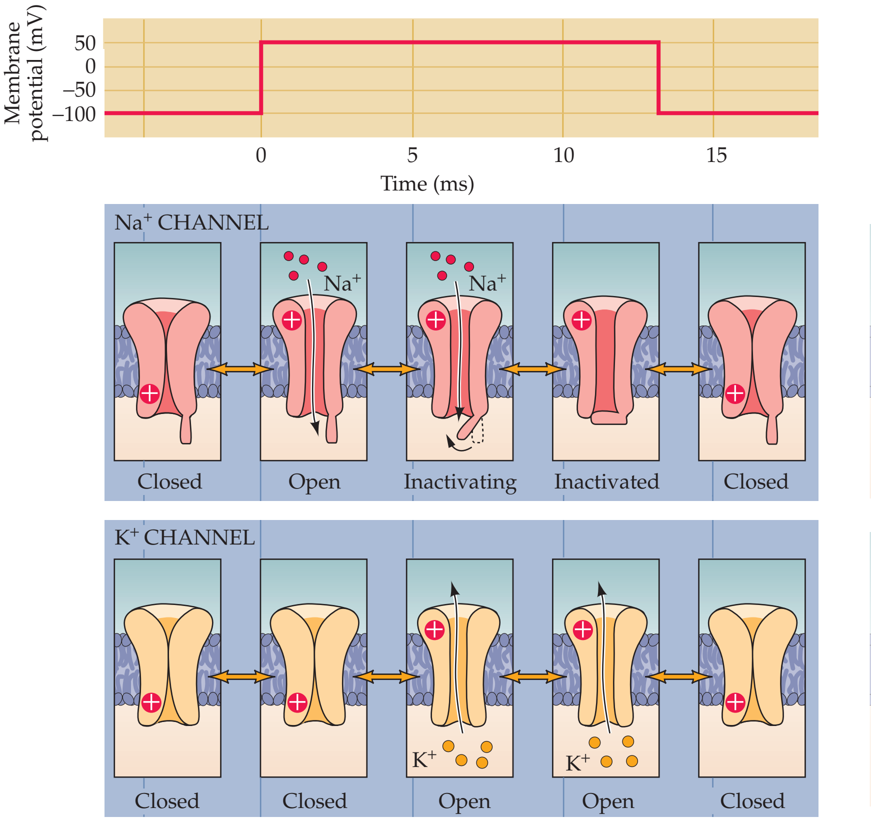

Figure 4.3 Functional states of voltage-gated Na$^+$ and K$^+$ channels. The gates of both channels are closed when the membrane potential is hyperpolarized. When the potential is depolarized, voltage sensors (indicated by +) allow the channel gates to open—first the Na$^+$ channels and then the K$^+$ channels. Na$^+$ channels also inactivate during prolonged depolarization, whereas many types of K$^+$ channels do not.

defined experimental systems, such as in cultured cells or frog oocytes (Box B), and then studied with patch clamping and other physiological techniques. Such studies have found many voltage-gated channels that respond to membrane potential in much the same way as the Na$^+$ and K$^+$ channels that underlie the action potential. Other channels, however, are gated by chemical signals that bind to extracellular or intracellular domains on these proteins and are insensitive to membrane voltage. Still others are sensitive to mechanical displacement, or to changes in temperature.

Further magnifying this diversity of ion channels are a number of mechanisms that can produce functionally different types of ion channels from a single gene. Ion channel genes contain a large number of coding regions that can be spliced together in different ways, giving rise to channel proteins that can have dramatically different functional properties. RNAs encoding ion channels also can be edited, modifying their base composition after transcription from the gene. For example, editing the RNA encoding of some receptors for the neurotransmitter glutamate (Chapter 6) changes a single amino acid within the receptor, which in turn gives rise to channels that differ in their selectivity for cations and in their conductance. Channel proteins can also undergo posttranslational modifications, such as phosphorylation by protein kinases (see Chapter 7), which can further change their functional characteristics. Thus, although the basic electrical signals of the nervous system are relatively stereotyped, the proteins responsible for generating these signals are remarkably diverse, conferring specialized signaling properties to many of the neuronal cell types that populate the nervous system. These channels also are involved in a broad range of neurological diseases.

Box B

Expression of Ion Channels in *Xenopus* Oocytes

Bridging the gap between the sequence of an ion channel gene and understanding channel function is a challenge. To meet this challenge, it is essential to have an experimental system in which the gene product can be expressed efficiently, and in which the function of the resulting channel can be studied with methods such as the patch clamp technique. Ideally, the vehicle for expression should be readily available, have few endogenous channels, and be large enough to permit mRNA and DNA to be microinjected with ease. Oocytes (immature eggs) from the clawed African frog, *Xenopus laevis* (Figure A), fulfill all these demands. These huge cells (approximately 1 mm in diameter; Figure B) are easily harvested from the female *Xenopus*. Work performed in the 1970s by John Gurdon, a developmental biologist, showed that injection of exogenous mRNA into frog oocytes causes them to synthesize foreign protein in prodigious quantities. In the early 1980s, Ricardo Miledi, Eric Barnard, and other neurobiologists demonstrated that *Xenopus* oocytes could express exogenous ion channels, and that physiological methods could be used to study the ionic currents generated by the newly-synthesized channels (Figure C).

As a result of these pioneering studies, heterologous expression experiments have now become a standard way of studying ion channels. The approach has been especially valuable in deciphering the relationship between channel structure and function. In such experiments, defined mutations (often affecting a single nucleotide) are made in the part of the channel gene that encodes a structure of interest; the resulting channel proteins are then expressed in oocytes to assess the functional consequences of the mutation.

The ability to combine molecular and physiological methods in a single cell system has made *Xenopus* oocytes a powerful experimental tool. Indeed, this system has been as valuable to contemporary studies of voltage-gated ion channels as the squid axon was to such studies in the 1950s and 1960s.

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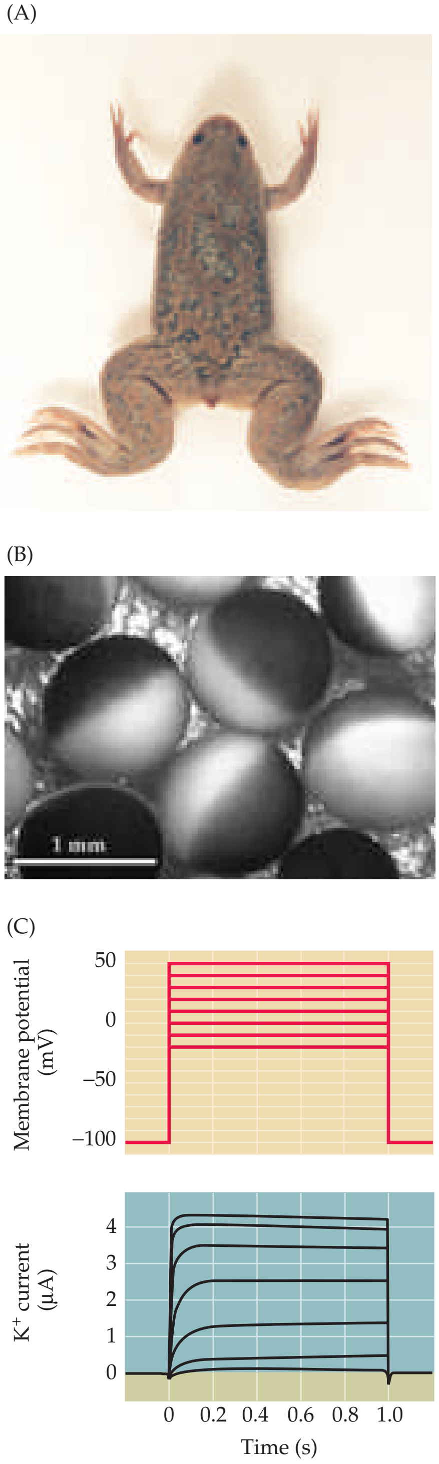


(A) The clawed African frog, *Xenopus laevis*. (B) Several oocytes from *Xenopus* highlighting the dark coloration of the original pole and the lighter coloration of the vegetal pole. (Courtesy of P. Reinhart.) (C) Results of a voltage clamp experiment showing K^+ currents produced following injection of K^+ channel mRNA into an oocyte. (After Gundersen et al., 1984.)

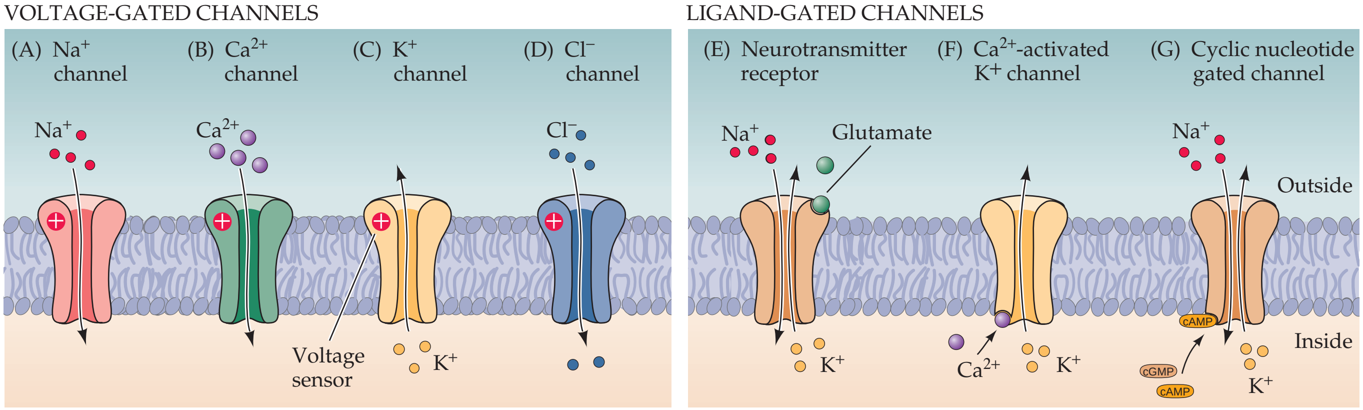
Voltage-Gated Ion Channels

Voltage-gated ion channels that are selectively permeable to each of the major physiological ions—Na^+, K^+, Ca^{2+}, and Cl^-—have now been discovered (Figure 4.4 A–D). Indeed, many different genes have been discovered for each type of voltage-gated ion channel. An example is the identification of 10 human Na^+ channel genes. This finding was unexpected because Na^+ channels from many different cell types have similar functional properties, consistent with their origin from a single gene. It is now clear, however, that all of these Na^+ channel genes (called SCN genes) produce proteins that differ in their structure, function, and distribution in specific tissues. For instance, in addition to the rapidly inactivating Na^+ channels discovered by Hodgkin and Huxley in squid axon, a voltage-sensitive Na^+ channel that does *not* inactivate has been identified in mammalian axons. As might be expected, this channel gives rise to action potentials of long duration and is a target of local anesthetics such as benzocaine and lidocaine.

Other electrical responses in neurons entail the activation of voltage-gated Ca^{2+} channels (Figure 4.4B). In some neurons, voltage-gated Ca^{2+} channels give rise to action potentials in much the same way as voltage-sensitive Na^+ channels. In other neurons, Ca^{2+} channels control the shape of action potentials generated primarily by Na^+ conductance changes. More generally, by affecting intracellular Ca^{2+} concentrations, the activity of Ca^{2+} channels regulates an enormous range of biochemical processes within cells (see Chapter 7). Perhaps the most important of the processes regulated by voltage-sensitive Ca^{2+} channels is the release of neurotransmitters at synapses (see Chapter 5). Given these crucial functions, it is perhaps not surprising that 16 different Ca^{2+} channel genes (called CACNA genes) have been identified. Like Na^+ channels, Ca^{2+} channels differ in their activation and inactivation properties, allowing subtle variations in both electrical and chemical signaling processes mediated by Ca^{2+}. As a result, drugs that block voltage-gated Ca^{2+} channels are especially valuable in treating a variety of conditions ranging from heart disease to anxiety disorders.

By far the largest and most diverse class of voltage-gated ion channels are the K^+ channels (Figure 4.4C). Nearly 100 K^+ channel genes are now known, and these fall into several distinct groups that differ substantially in their activation, gating, and inactivation properties. Some take minutes to inactivate, as in the case of squid axon K^+ channels studied by Hodgkin and Huxley (Figure 4.5A). Others inactivate within milliseconds, as is typical of most voltage-gated Na^+ channels (Figure 4.5B). These properties influence the

Figure 4.4 Types of voltage-gated ion channels. Examples of voltage-gated channels include those selectively permeable to Na^+ (A), Ca^{2+} (B), K^+ (C), and Cl^- (D). Ligand-gated ion channels include those activated by the extracellular presence of neurotransmitters, such as glutamate (E). Other ligand-gated channels are activated by intracellular second messengers, such as Ca^{2+} (F) or the cyclic nucleotides, cAMP and cGMP (G).



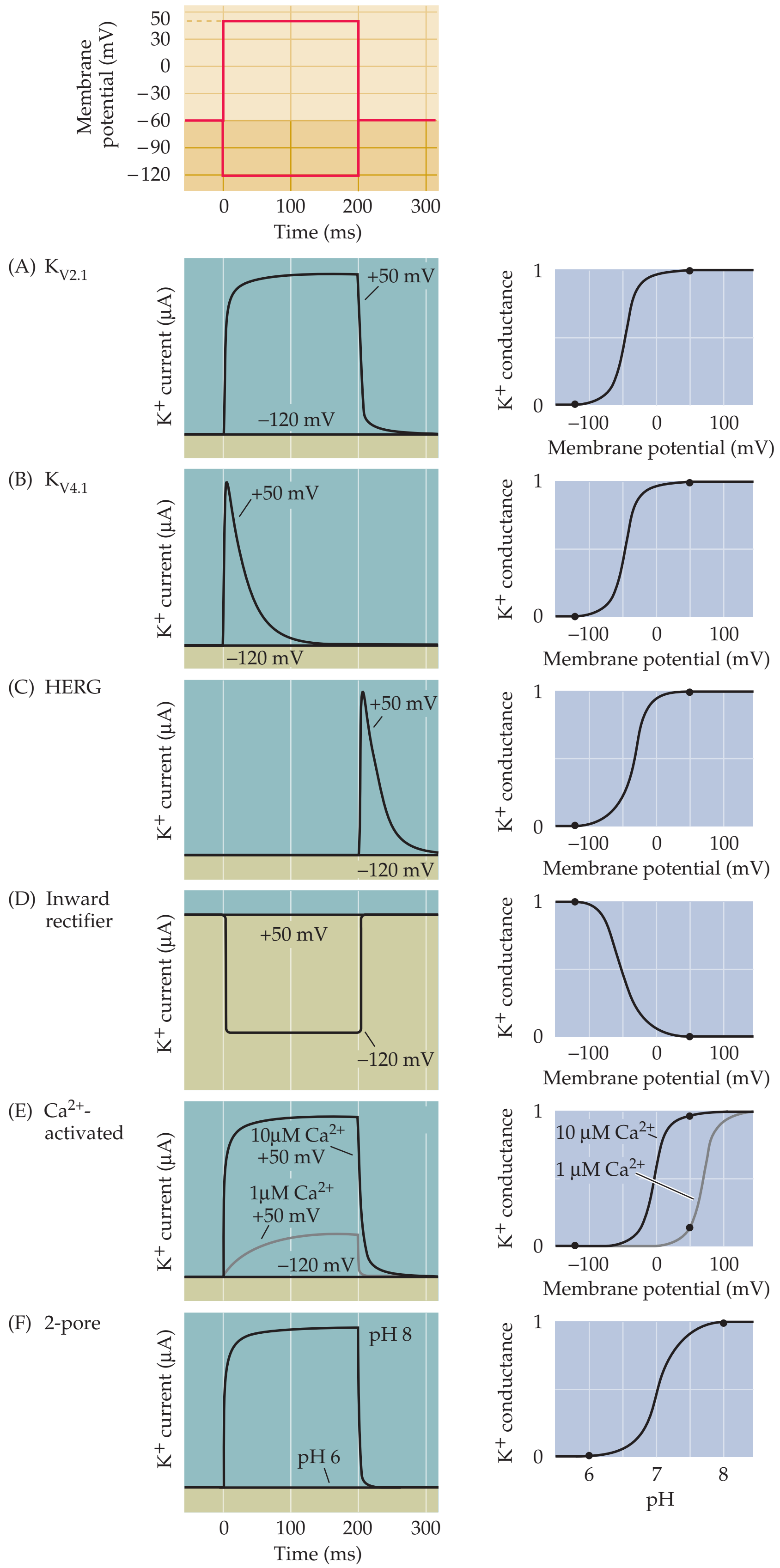


Figure 4.5 Diverse properties of K^+ channels. Different types of K^+ channels were expressed in *Xenopus* oocytes (see Box B), and the voltage clamp method was used to change the membrane potential (top) and measure the resulting currents flowing through each type of channel. These K^+ channels vary markedly in their gating properties, as evident in their currents (left) and conductances (right). (A) $K_{V2.1}$ channels show little inactivation and are closely related to the delayed rectifier K^+ channels involved in action potential repolarization. (B) $K_{V4.1}$ channels inactivate during a depolarization. (C) HERG channels inactivate so rapidly that current flows only when inactivation is rapidly removed at the end of a depolarization. (D) Inward rectifying K^+ channels allow more K^+ current to flow at hyperpolarized potentials than at depolarized potentials. (E) Ca^{2+}-activated K^+ channels open in response to intracellular Ca^{2+} ions and, in some cases, membrane depolarization. (F) K^+ channels with two pores usually respond to chemical signals, such as pH, rather than changes in membrane potential.

duration and rate of action potential firing, with important consequences for axonal conduction and synaptic transmission. Perhaps the most important function of K^+ channels is the role they play in generating the resting membrane potential (see Chapter 2). At least two families of K^+ channels that are open at substantially negative membrane voltage levels contribute to setting the resting membrane potential (Figure 4.5D).

Finally, several types of voltage-gated Cl^- channel have been identified (see Figure 4.4D). These channels are present in every type of neuron, where they control excitability, contribute to the resting membrane potential, and help regulate cell volume.

Ligand-Gated Ion Channels

Many types of ion channels respond to chemical signals (ligands) rather than to changes in the membrane potential (Figure 4.4E–G). The most important of these **ligand-gated ion channels** in the nervous system is the class activated by binding neurotransmitters (Figure 4.4E). These channels are essential for synaptic transmission and other forms of cell-cell signaling phenomena discussed in Chapters 5–7. Whereas the voltage-gated ion channels underlying the action potential typically allow only one type of ion to permeate, channels activated by extracellular ligands are usually less selective, allowing two or more types of ions to pass through the channel pore.

Other ligand-gated channels are sensitive to chemical signals arising within the cytoplasm of neurons (see Chapter 7), and can be selective for specific ions such as K^+ or Cl^-, or permeable to all physiological cations. Such channels are distinguised by ligand-binding domains on their *intracellular* surfaces that interact with second messengers such as Ca^{2+}, the cyclic nucleotides cAMP and cGMP, or protons. Examples of channels that respond to intracellular cues include Ca^{2+}-activated K^+ channels (Figure 4.4.F), the cyclic nucleotide gated cation channel (Figure 4.4G), or acid-sensing ion channels (ASICs). The main function of these channels is to convert intracellular chemical signals into electrical information. This process is particularly important in sensory transduction, where channels gated by cyclic nucleotides convert odors and light, for example, into electrical signals. Although many of these ligand-gated ion channels are located in the cell surface membrane, others are in membranes of intracellular organelles such as mitochondria or the endoplasmic reticulum . Some of these latter channels are selectively permeable to Ca^{2+} and regulate the release of Ca^{2+} from the lumen of the endoplasmic reticulum into the cytoplasm, where this second messenger can then trigger a spectrum of cellular responses such as described in Chapter 7.

Stretch- and Heat-Activated Channels

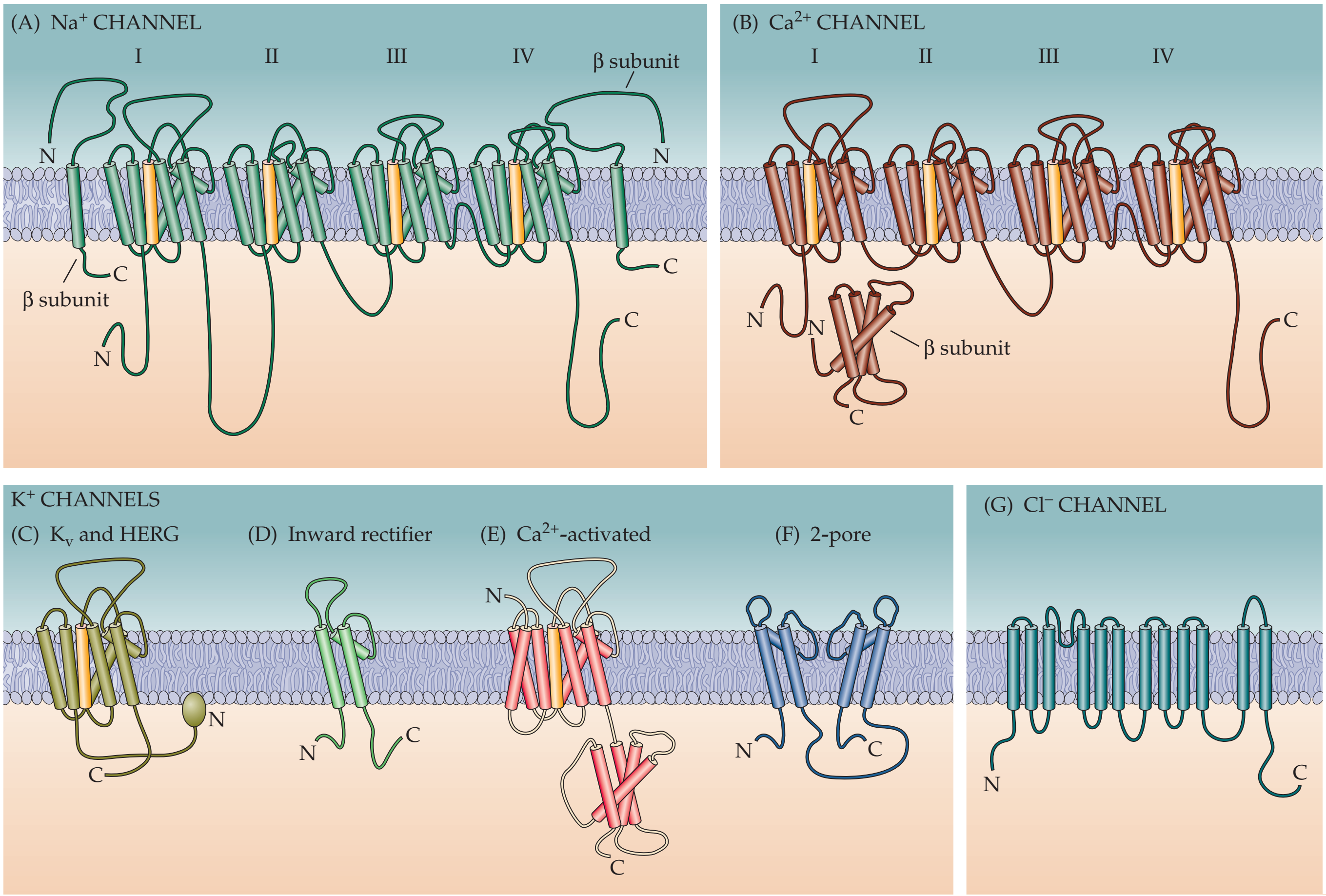
Still other ion channels respond to heat or membrane deformation. Heat-activated ion channels, such as some members of the transient receptor potential (TRP) gene family, contribute to the sensations of pain and temperature and help mediate inflammation (see Chapter 9). These channels are often specialized to detect specific temperature ranges, and some are even activated by cold. Other ion channels respond to mechanical distortion of the plasma membrane and are the basis of stretch receptors and neuromuscular stretch reflexes (see Chapters 8, 15 and 16). A specialized form of these channels enables hearing by allowing auditory hair cells to respond to sound waves (see Chapter 12).

In summary, this tremendous variety of ion channels allows neurons to generate electrical signals in response to changes in membrane potential, synaptic input, intracellular second messengers, light, odors, heat, sound, touch, and many other stimuli.

The Molecular Structure of Ion Channels

Understanding the physical structure of ion channels is obviously the key to sorting out how they actually work. Until recently, most information about channel structure was derived indirectly from studies of the amino acid composition and physiological properties of these proteins. For example, a great deal has been learned by exploring the functions of particular amino acids within the proteins using **mutagenesis** and the expression of such channels in *Xenopus* oocytes (see Box B). Such studies have discovered a general transmembrane architecture common to all the major ion channel families. Thus, these molecules are all integral membrane proteins that span the plasma membrane repeatedly. Na^+ (and Ca^{2+}) channel proteins, consist of repeating motifs of 6 membrane-spanning regions that are repeated 4 times, for a total of 24 transmembrane regions (Figure 4.6A,B). Na^+ (or Ca^{2+}) channels can be produced by just one of these proteins, although other accessory proteins, called β subunits, can regulate the function of these channels. K^+ channel proteins typically span the membrane six times (Figure 4.6C),

Figure 4.6 Topology of the principal subunits of voltage-gated Na^+, Ca^{2+}, K^+, and Cl^- channels. Repeating motifs of Na^+ (A) and Ca^{2+} (B) channels are labeled I, II, III, and IV; (C–F) K^+ channels are more diverse. In all cases, four subunits combine to form a functional channel. (G) Chloride channels are structurally distinct from all other voltage-gated channels.



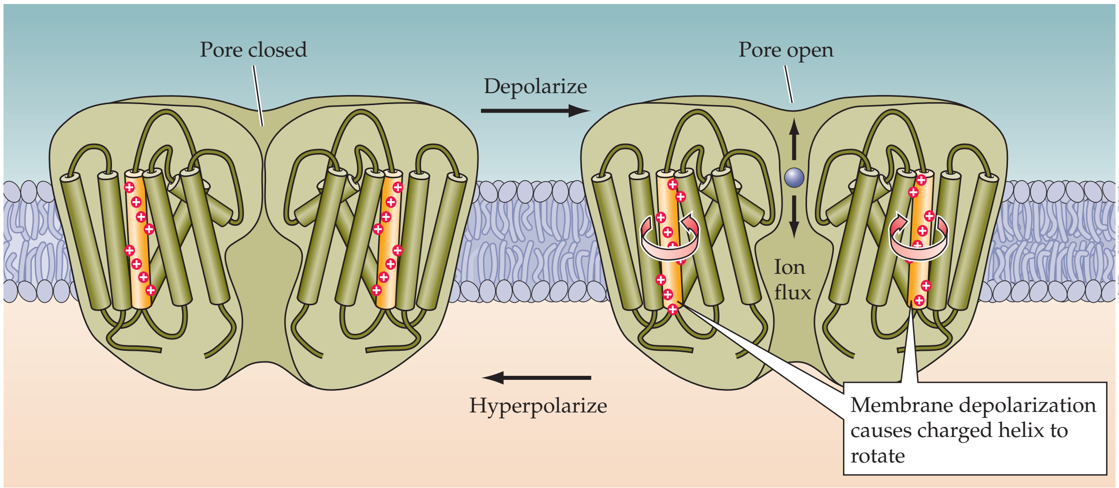
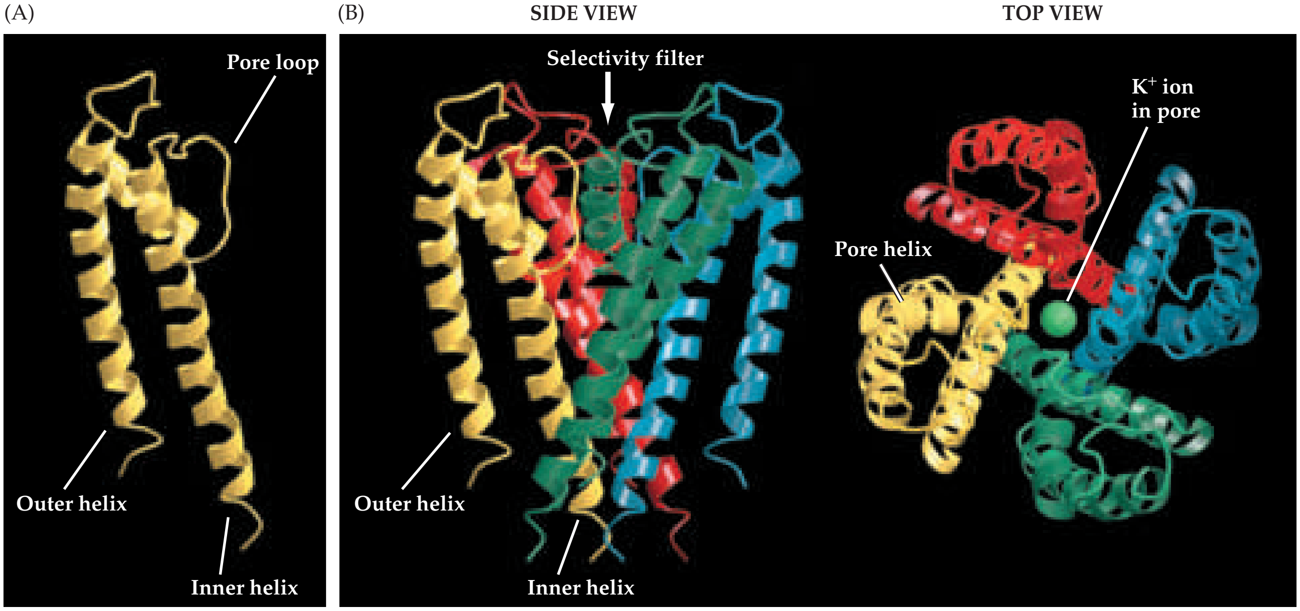


Figure 4.7 A charged voltage sensor permits voltage-dependent gating of ion channels. The process of voltage activation may involve the rotation of a positively charged transmembrane domain. This movement causes a change in the conformation of the pore loop, enabling the channel to conduct specific ions.

though there are some K$^+$ channels, such as a bacterial channel and some mammalian channels, that span the membrane only twice (Figure 4.6D), and others that span the membrane four times (Figure 4.6F) or seven times (Figure 4.6E). Each of these K$^+$ channel proteins serves as a channel subunit, with 4 of these subunits typically aggregating to form a single functional ion channel.

Other imaginative mutagenesis experiments have provided information about how these proteins function. Two membrane-spanning domains of all ion channels appear to form a central **pore** through which ions can diffuse, and one of these domains contains a protein loop that confers an ability to selectivity allow certain ions to diffuse through the channel pore (Figure 4.7). As might be expected, the amino acid composition of the pore loop differs among channels that conduct different ions. These distinct structural features of channel proteins also provide unique binding sites for drugs and for various neurotoxins known to block specific subclasses of ion channels (Box C). Furthermore, many voltage gated ion channels contain a distinct type of transmembrane helix containing a number of positively charged amino acids along one face of the helix (Figures 4.6 and 4.7). This structure evidently serves as a sensor that detects changes in the electrical potential across the membrane. Membrane depolarization influences the charged amino acids such that the helix undergoes a conformational change, which in turn allows the channel pore to open. One suggestion is that the helix rotates to cause the pore to open (Figure 4.7). Other types of mutagenesis experiments have demonstrated that one end of certain K$^+$ channels plays a key role in channel inactivation. This intracellular structure (labeled “N” in Figure 4.6C) can plug the channel pore during prolonged depolarization.

More recently, very direct information about the structural underpinnings of ion channel function has come from **X-ray crystallography** studies of bacterial K$^+$ channels (Figure 4.8). This molecule was chosen for analysis because the large quantity of channel protein needed for crystallography could be obtained by growing large numbers of bacteria expressing this molecule. The results of such studies showed that the channel is formed by subunits that each cross the plasma membrane twice; between these two membrane-spanning structures is a loop that inserts into the plasma membrane (Figure 4.8A). Four of these subunits are assembled together to form a chan-


(A)
Pore loop
Outer helix
Inner helix
(B)
SIDE VIEW
Selectivity filter
Outer helix
Inner helix
TOP VIEW
K+ ion in pore
Pore helix

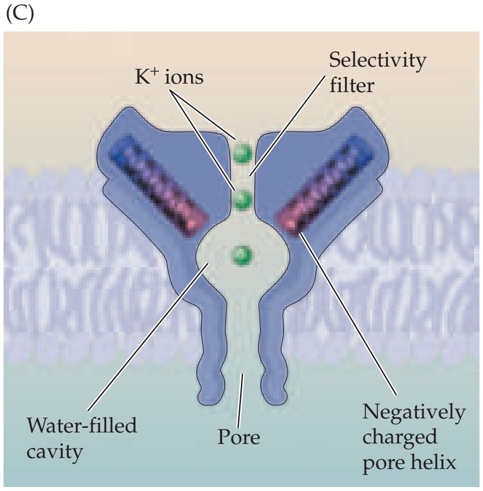

(C)
K+ ions
Selectivity filter
Water-filled cavity
Pore
Negatively charged pore helix

Figure 4.8 Structure of a simple bacterial K^+ channel determined by crystallography. (A) Structure of one subunit of the channel, which consists of two membrane-spanning domains and a pore loop that inserts into the membrane. (B) Three-dimensional arrangement of four subunits (each in a different color) to form a K^+ channel. The top view illustrates a K^+ ion (green) within the channel pore. (C) The permeation pathway of the K^+ channel consists of a large aqueous cavity connected to a narrow selectivity filter. Helical domains of the channel point negative charges (red) toward this cavity, allowing K^+ ions (green) to become dehydrated and then move through the selectivity filter. (A, B from Doyle et al., 1998; C after Doyle et al., 1998.)

nel (Figure 4.8B). In the center of the assembled channel is a narrow opening through the protein that allows K^+ to flow across the membrane. This opening is the channel pore and is formed by the protein loop, as well as by the membrane-spanning domains. The structure of the pore is well suited for conducting K^+ ions (Figure 4.8C). The narrowest part is near the outside mouth of the channel and is so constricted that only a non-hydrated K^+ ion can fit through the bottleneck. Larger cations, such as Cs^+, cannot traverse this region of the pore, and smaller cations such as Na^+ cannot enter the pore because the "walls" of the pore are too far apart to stabilize a dehydrated Na^+ ion. This part of the channel complex is responsible for the selective permeability to K^+ and is therefore called the **selectivity filter**. The sequence of amino acids making up part of this selectivity filter is often referred to as the K^+ channel "signature sequence". Deeper within the channel is a water-filled cavity that connects to the interior of the cell. This cavity evidently collects K^+ from the cytoplasm and, utilizing negative charges from the protein,

Box C

Toxins That Poison Ion Channels

Given the importance of Na$^+$ and K$^+$ channels for neuronal excitation, it is not surprising that a number of organisms have evolved channel-specific toxins as mechanisms for self-defense or for capturing prey. A rich collection of natural toxins selectively target the ion channels of neurons and other cells. These toxins are valuable not only for survival, but for studying the function of cellular ion channels. The best-known channel toxin is *tetrodotoxin*, which is produced by certain puffer fish and other animals. Tetrodotoxin produces a potent and specific obstruction of the Na$^+$ channels responsible for action potential generation, thereby paralyzing the animals unfortunate enough to ingest it. *Saxitoxin*, a chemical homologue of tetrodotoxin produced by dinoflagellates, has a similar action on Na$^+$ channels. The potentially lethal effects of eating shellfish that have ingested these "red tide" dinoflagellates are due to the potent neuronal actions of saxitoxin.

Scorpions paralyze their prey by injecting a potent mix of peptide toxins that also affect ion channels. Among these are the α-*toxins*, which slow the inactivation of Na$^+$ channels (Figure A1); exposure of neurons to these toxins prolongs the action potential (Figure A2), thereby scrambling information flow within the nervous system of the soon-to-be-devoured victim. Other peptides in scorpion venom, called β-*toxins*, shift the voltage dependence of Na$^+$ channel activation (Figure B). These toxins cause Na$^+$ channels to open at potentials much more negative than normal, disrupting action potential generation. Some alkaloid toxins combine these actions, both removing inactivation *and* shifting activation of Na$^+$ channels. One such toxin is *batrachotoxin*, produced by a species of frog; some tribes of South American Indians use this poison on their arrow tips. A number of plants produce similar toxins, including *aconitine*, from buttercups; *veratridine*, from lilies; and a number of insecticidal toxins produced by plants such as chrysanthemums and rhododendrons.

Potassium channels have also been targeted by toxin-producing organisms. Peptide toxins affecting K$^+$ channels include *dendrotoxin*, from wasps; *apamin*, from bees; and *charybdotoxin*, yet another toxin produced by scorpions. All of these toxins block K$^+$ channels as their primary action; no toxin is known to affect the activation or inactivation of these channels, although such agents may simply be awaiting discovery.

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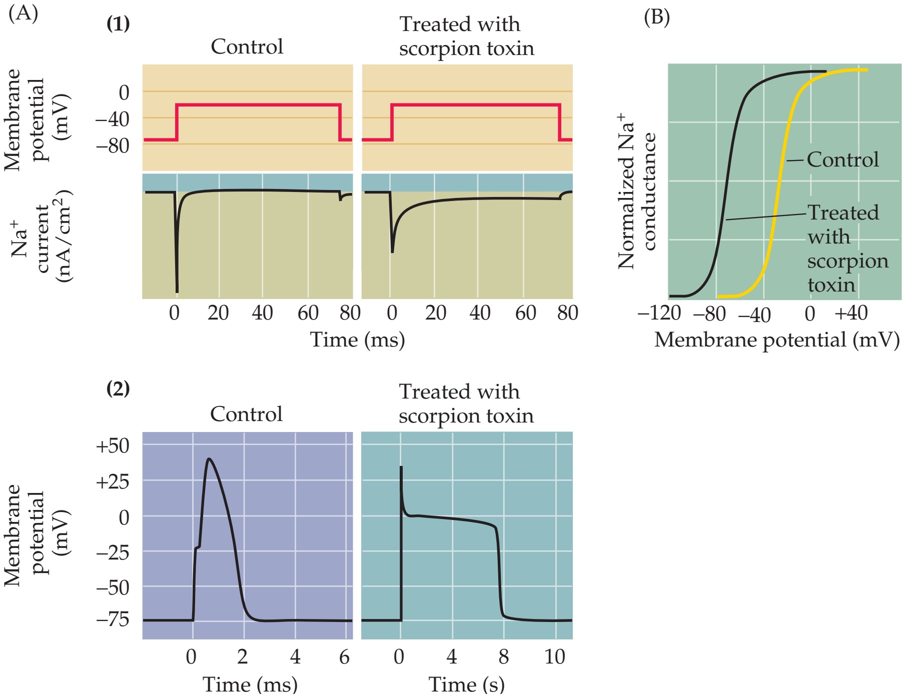


(A) Effects of toxin treatment on frog axons. (1) α-Toxin from the scorpion *Leiurus quinquestriatus* prolongs Na$^+$ currents recorded with the voltage clamp method. (2) As a result of the increased Na$^+$ current, α-toxin greatly prolongs the duration of the axonal action potential. Note the change in timescale after treating with toxin. (B) Treatment of a frog axon with β-toxin from another scorpion, *Centruroides sculpturatus*, shifts the activation of Na$^+$ channels, so that Na$^+$ conductance begins to increase at potentials much more negative than usual. (A after Schmidt and Schmidt, 1972; B after Cahalan, 1975.)

allows K^+ ions to become dehydrated so they can enter the selectivity filter. These "naked" ions are then able to move through four K^+ binding sites within the selectivity filter to eventually reach the extracellular space (recall that the normal concentration gradient drives K^+ out of cells). On average, two K^+ ions reside within the selectivity filter at any moment, with electrostatic repulsion between the two ions helping to speed their transit through the selectivity filter, thereby permitting rapid ion flux through the channel.

Crystallographic studies have also determined the structure of the **voltage sensor** in another type of bacterial K^+ channel. Such studies indicate that the sensor is at the interface between proteins and lipid on the cytoplasmic surface of the channel, leading to the suggestion that the sensor is a paddle-like structure that moves through the membrane to gate the opening of the channel pore (Figure 4.9A), rather than being a rotating helix buried within the ion channel protein (as in Figure 4.7). Crystallographic work has also revealed the molecular basis of the rapid transitions between the closed and the open state of the channel during channel gating. By comparing data from K^+ channels crystallized in what is believed to be closed and open conformations (Figure 4.9B), it appears that channels gate by a conformational change in one of the transmembrane helices lining the channel pore. Producing a "kink" in one of these helices increases the opening from the central water-filled pore to the intracellular space, thereby permitting ion fluxes.

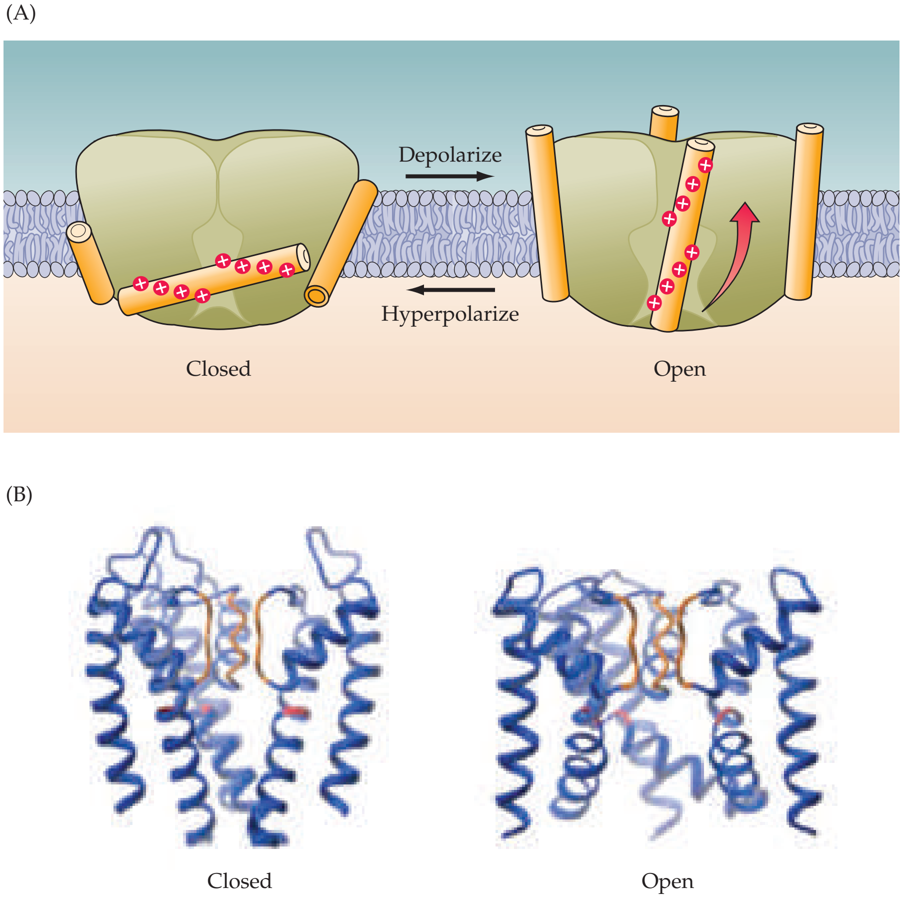


Figure 4.9 Structural features of K^+ channel gating. (A) Voltage sensing may involve paddle-like structures of the channel. These paddles reside within the lipid bilayer of the plasma membrane and may respond to changes in membrane potential by moving through the membrane. The gating charges that sense membrane potential are indicated by red "plus" signs. (B) Structure of K^+ channels in closed (left) and open (right) conformations. Three of the four channel subunits are shown. Opening of the pore of the channel involves kinking of a transmembrane domain at the point indicated in red, which then dilates the pore. (A after Jiang et al., 2003; B after MacKinnon, 2003).

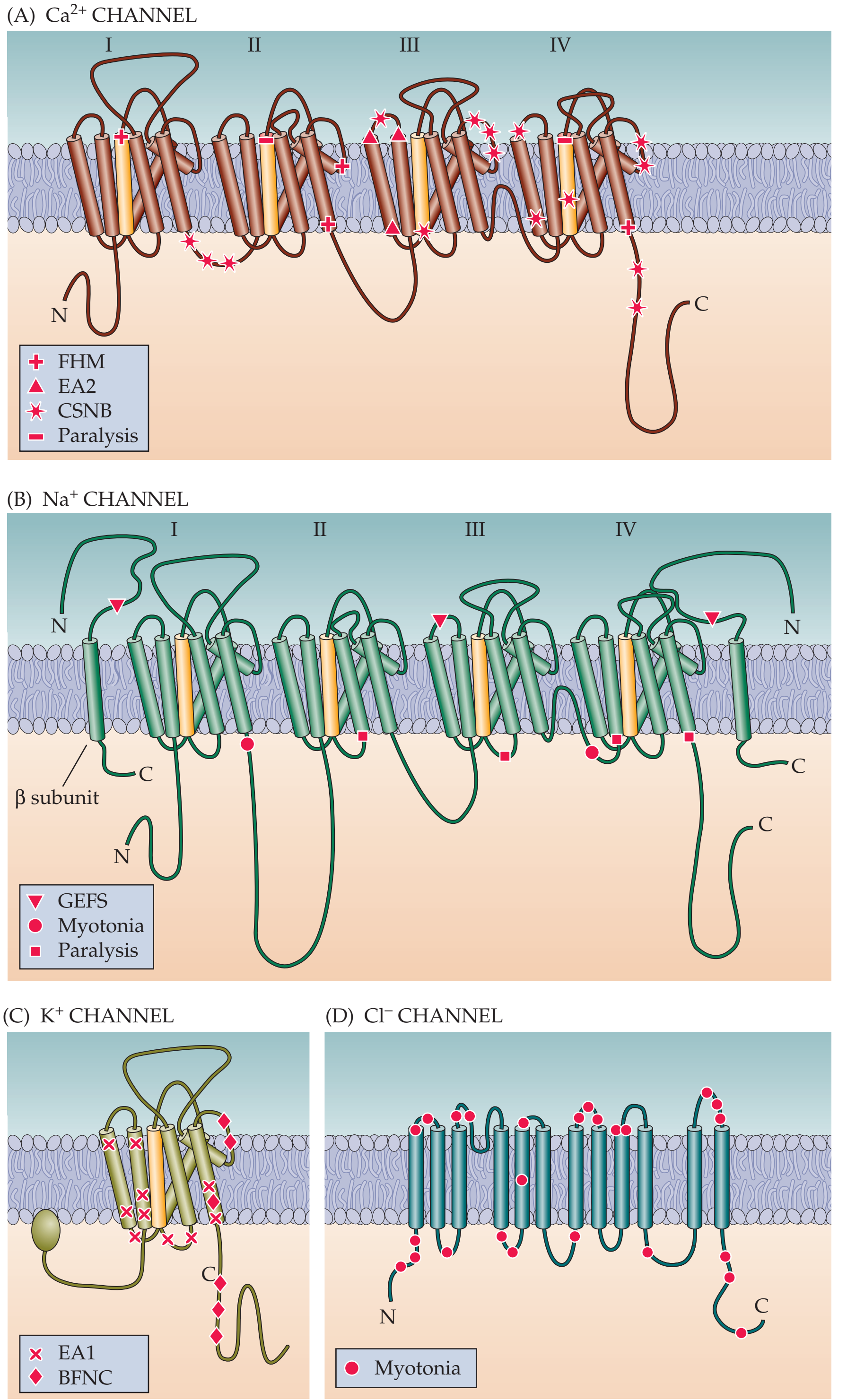
Box D

Diseases Caused by Altered Ion Channels

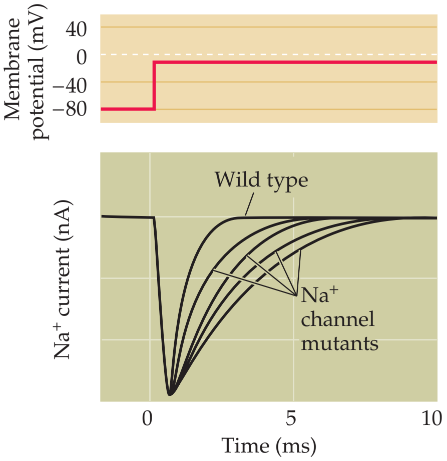
Several genetic diseases, collectively called *channelopathies*, result from small but critical alterations in ion channel genes. The best-characterized of these diseases are those that affect skeletal muscle cells. In these disorders, alterations in ion channel proteins produce either myotonia (muscle stiffness due to excessive electrical excitability) or paralysis (due to insufficient muscle excitability). Other disorders arise from ion channel defects in heart, kidney, and the inner ear.

Channelopathies associated with ion channels localized in brain are much more difficult to study. Nonetheless, voltage-gated Ca^{2+} channels have recently been implicated in a range of neurological diseases. These include episodic ataxia, spinocerebellar degeneration, night blindness, and migraine headaches. F*amilial hemiplegic migraine* (FHM) is characterized by migraine attacks that typically last one to three days. During such episodes, patients experience severe headaches and vomiting. Several mutations in a human Ca^{2+} channel have been identified in families with FHM, each having different clinical symptoms. For example, a mutation in the pore-forming region of the channel produces hemiplegic migraine with progressive cerebellar ataxia, whereas other mutations cause only the usual FHM symptoms. How these altered Ca^{2+} channel properties lead to migraine attacks is not known.

Episodic ataxia type 2 (EA2) is a neurological disorder in which affected individuals suffer recurrent attacks of abnormal limb movements and severe ataxia. These problems are sometimes accompa-



Genetic mutations in (A) Ca^{2+} channels, (B) Na^{+} channels, (C) K^{+} channels, and (D) Cl^{-} channels that result in diseases. Red regions indicate the sites of these mutations; the red circles indicate mutations. (After Lehmann-Horn and Jurkat-Kott, 1999.)



Mutations in Na$^+$ channels slow the rate of inactivation of Na$^+$ currents. (After Barchi, 1995.)

nied by vertigo, nausea, and headache. Usually, attacks are precipitated by emotional stress, exercise, or alcohol and last for a few hours. The mutations in EA2 cause Ca^{2+} channels to be truncated at various sites, which may cause the clinical manifestations of the disease by preventing the normal assembly of Ca^{2+} channels in the membrane.

X-linked *congenital stationary night blindness* (CSNB) is a recessive retinal disorder that causes night blindness, decreased visual acuity, myopia, nystagmus, and strabismus. Complete CSNB causes retinal rod photoreceptors to be nonfunctional. Incomplete CSNB causes subnormal (but measurable) functioning of both rod and cone photoreceptors. Like EA2, the incomplete type of CSNB is caused by mutations producing truncated Ca^{2+} channels. Abnormal retinal function may arise from decreased Ca^{2+} currents and neurotransmitter release from photoreceptors (see Chapter 11).

A defect in brain Na$^+$ channels causes *generalized epilepsy with febrile seizures* (GEFS) that begins in infancy and usually continues through early puberty. This defect has been mapped to two mutations: one on chromosome 2 that encodes an α subunit for a voltage-gated Na$^+$ channel, and the other on chromosome 19 that encodes a Na$^+$ channel β subunit. These mutations cause a slowing of Na$^+$ channel inactivation (see figure above), which may explain the neuronal hyperexcitability underlying GEFS.

Another type of seizure, *benign familial neonatal convulsion* (BFNC), is due to K$^+$ channel mutations. This disease is characterized by frequent brief seizures commencing within the first week of life and disappearing spontaneously within a few months. The mutation has been mapped to at least two voltage-gated K$^+$ channel genes. A reduction in K$^+$ current flow through the mutated channels probably accounts for the hyperexcitability associated with this defect. A related disease, episodic ataxia type 1 (EA1), has been linked to a defect in another type of voltage-gated K$^+$ channel. EA1 is characterized by brief episodes of ataxia. Mutant channels inhibit the function of other, non-mutant K$^+$ channels and may produce clinical symptoms by impairing action potential repolarization. Mutations in the K$^+$ channels of cardiac muscle are responsible for the irregular heartbeat of patients with long Q-T syndrome. Numerous genetic disorders affect the voltage-gated channels of skeletal muscle and are responsible for a host of muscle diseases that either cause muscle weakness (*paralysis*) or muscle contraction (*myotonia*).

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In short, ion channels are integral membrane proteins with characteristic features that allow them to assemble into multimolecular aggregates. Collectively, these structures allow channels to conduct ions, sense the transmembrane potential, to inactivate, and to bind to various neurotoxins. A combination of physiological, molecular biological and crystallographic studies has begun to provide a detailed physical picture of K$^+$ channels. This work has now provided considerable insight into how ions are conducted from one side of the plasma membrane to the other, how a channel can be selectively permeable to a single type of ion, how they are able to sense changes in membrane voltage, and how they gate the opening of their pores. It is likely that other types of ion channels will be similar in their functional architecture. Finally, this sort of work has illuminated how mutations in ion channel genes can lead to a variety of neurological disorders (Box D).

Active Transporters Create and Maintain Ion Gradients

Up to this point, the discussion of the molecular basis of electrical signaling has taken for granted the fact that nerve cells maintain ion concentration gradients across their surface membranes. However, none of the ions of physiological importance (Na^+, K^+, Cl^-, and Ca^{2+}) are in electrochemical equilibrium. Because channels produce electrical effects by allowing one or more of these ions to diffuse down their electrochemical gradients, there would be a gradual dissipation of these concentration gradients unless nerve cells could restore ions displaced during the current flow that occurs as a result of both neural signaling and the continual ionic leakage that occurs at rest. The work of generating and maintaining ionic concentration gradients for particular ions is carried out by a group of plasma membrane proteins known as **active transporters**.

Active transporters carry out this task by forming complexes with the ions that they are translocating. The process of ion binding and unbinding for transport typically requires several milliseconds. As a result, ion translocation by active transporters is much slower than ion movement through channels: Recall that ion channels can conduct thousands of ions across a membrane each millisecond. In short, active transporters gradually store energy in the form of ion concentration gradients, whereas the opening of ion channels rapidly dissipates this stored energy during relatively brief electrical signaling events.

Several types of active transporter have now been identified (Figure 4.10). Although the specific jobs of these transporters differ, all must translocate ions against their electrochemical gradients. Moving ions uphill requires the consumption of energy, and neuronal transporters fall into two classes based on their energy sources. Some transporters acquire energy directly from the hydrolysis of ATP and are called **ATPase pumps** (Figure 4.10, left)**.** The most prominent example of an ATPase pump is the **Na^+ pump** (or, more properly, the Na^+/K^+ ATPase pump), which is responsible for maintaining transmembrane concentration gradients for both Na^+ and K^+ (Figure 4.10A). Another is the Ca^{2+} pump, which provides one of the main mechanisms for removing Ca^{2+} from cells (Figure 4.10B). The second class of active transporter does not use ATP directly, but depends instead on the electrochemical gradients of other ions as an energy source. This type of transporter carries one or more ions *up* its electrochemical gradient while simultaneously taking another ion (most often Na^+) *down* its gradient. Because at least two species of ions are

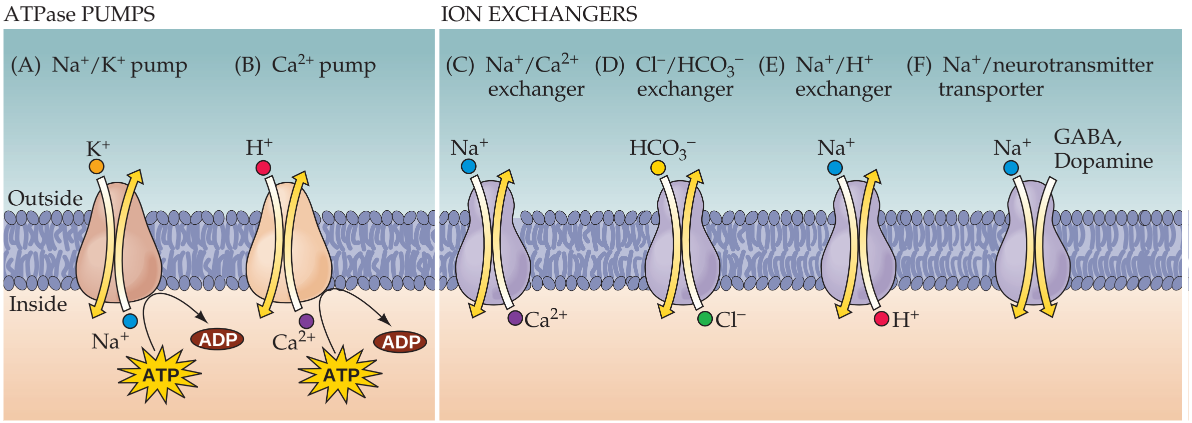


Figure 4.10 Examples of ion transporters found in cell membranes. (A,B) Some transporters are powered by the hydrolysis of ATP (ATPase pumps), whereas others (C–F) use the electrochemical gradients of co-transported ions as a source of energy (ion exchangers).

involved in such transactions, these transporters are usually called **ion exchangers** (Figure 4.10, right). An example of such a transporter is the Na^+/Ca^{2+} exchanger, which shares with the Ca^{2+} pump the important job of keeping intracellular Ca^{2+} concentrations low (Figure 4.10C). Another exchanger in this category regulates both intracellular Cl^- concentration and pH by swapping intracellular Cl^- for another extracellular anion, bicarbonate (Figure 4.10D). Other ion exchangers, such as the Na^+/H^+ exchanger (Figure 4.10E), also regulate intracellular pH, in this case by acting directly on the concentration of H^+. Yet other ion exchangers are involved in transporting neurotransmitters into synaptic terminals (Figure 4.10F), as described in Chapter 6. Although the electrochemical gradient of Na^+ (or other counter ions) is the proximate source of energy for ion exchangers, these gradients ultimately depend on the hydrolysis of ATP by ATPase pumps, such as the Na^+/K^+ ATPase pump.

Functional Properties of the Na^+/K^+ Pump

Of these various transporters, the best understood is the Na^+/K^+ pump. The activity of this pump is estimated to account for 20–40% of the brain's energy consumption, indicating its importance for brain function. The Na^+ pump was first discovered in neurons in the 1950s, when Richard Keynes at Cambridge University used radioactive Na^+ to demonstrate the energy-dependent efflux of Na^+ from squid giant axons. Keynes and his collaborators found that this efflux ceased when the supply of ATP in the axon was interrupted by treatment with metabolic poisons (Figure 4.11A, point 4). Other conditions that lower intracellular ATP also prevent Na^+ efflux. These experiments showed that removing intracellular Na^+ requires cellular metabolism. Further studies with radioactive K^+ demonstrated that Na^+ efflux is associated with simultaneous, ATP-dependent influx of K^+. These opposing fluxes of Na^+ and K^+ are operationally inseparable: Removal of external K^+ greatly reduces Na^+ efflux (Figure 4.11, point 2), and vice versa. These energy-dependent movements of Na^+ and K^+ implicated an ATP-hydrolyzing Na^+/K^+ pump in the generation of the transmembrane gradients of both Na^+ and K^+. The exact mechanism responsible for these fluxes of Na^+ and K^+ is still not entirely clear, but the pump is thought to alternately shuttle these ions across the membranes in a cycle fueled by the transfer of a phosphate group from ATP to the pump protein (Figure 4.11B).

Additional quantitative studies of the movements of Na^+ and K^+ indicate that the two ions are not pumped at identical rates: The K^+ influx is only about two-thirds the Na^+ efflux. Thus, the pump apparently transports two K^+ into the cell for every three Na^+ that are removed (see Figure 4.11B). This stoichiometry causes a net loss of one positively charged ion from inside of the cell during each round of pumping, meaning that the pump generates an electrical current that can hyperpolarize the membrane potential. For this reason, the Na^+/K^+ pump is said to be **electrogenic**. Because pumps act much more slowly than ion channels, the current produced by the Na^+/K^+ pump is quite small. For example, in the squid axon, the net current generated by the pump is less than 1% of the current flowing through voltage-gated Na^+ channels and affects the resting membrane potential by only a millivolt or less.

Although the electrical current generated by the activity of the Na^+/K^+ pump is small, under special circumstances the pump can significantly influence the membrane potential. For instance, prolonged stimulation of

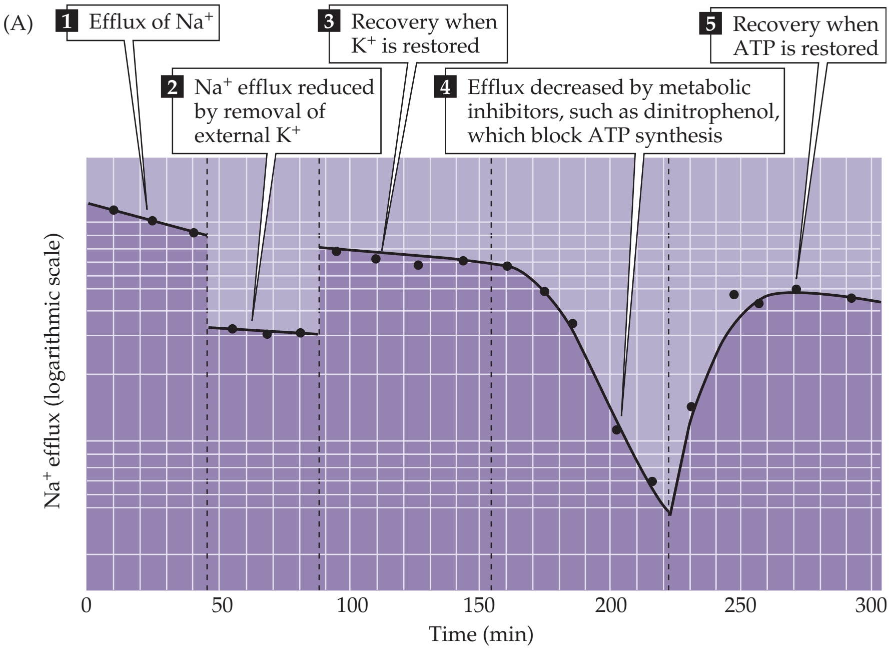


Figure 4.11 Ionic movements due to the Na^+/K^+ pump. (A) Measurement of radioactive Na^+ efflux from a squid giant axon. This efflux depends on external K^+ and intracellular ATP. (B) A model for the movement of ions by the Na^+/K^+ pump. Uphill movements of Na^+ and K^+ are driven by ATP, which phosphorylates the pump. These fluxes are asymmetrical, with three Na^+ carried out for every two K^+ brought in. (A after Hodgkin and Keynes, 1955; B after Lingrel et al., 1994.)

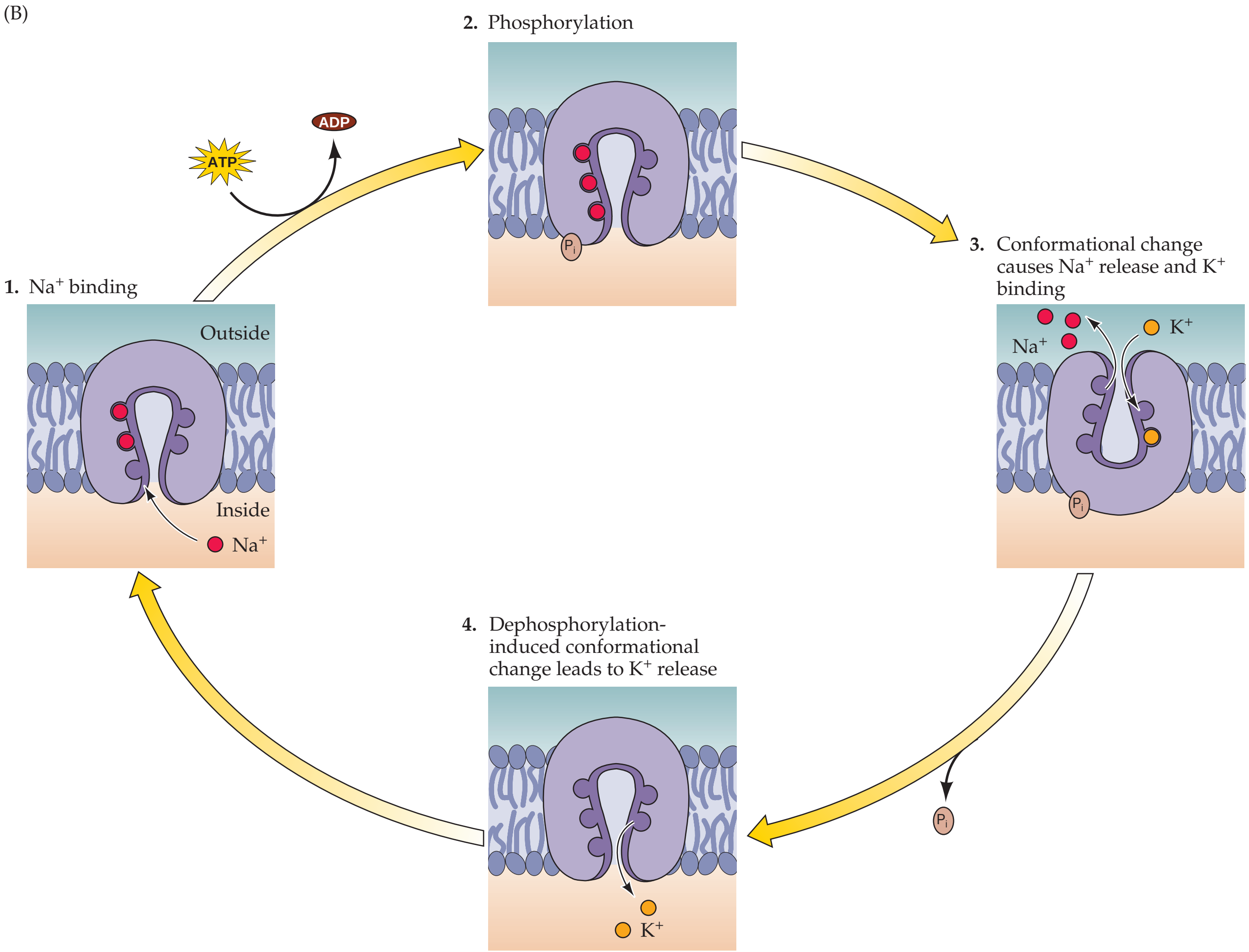
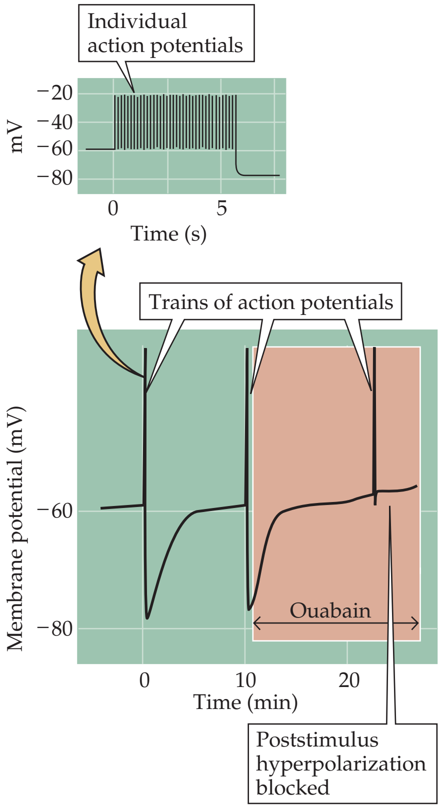

(B)
2. Phosphorylation
ATP
ADP
Pi
3. Conformational change causes Na⁺ release and K⁺ binding
Na⁺
K⁺
Pi
1. Na⁺ binding
Outside
Inside
Na⁺
4. Dephosphorylation-induced conformational change leads to K⁺ release
Pi
K⁺

Figure 4.12 The electrogenic transport of ions by the Na^+/K^+ pump can influence membrane potential. Measurements of the membrane potential of a small unmyelinated axon show that a train of action potentials is followed by a long-lasting hyperpolarization. This hyperpolarization is blocked by ouabain, indicating that it results from the activity of the Na^+/K^+ pump. (After Rang and Ritchie, 1968.)

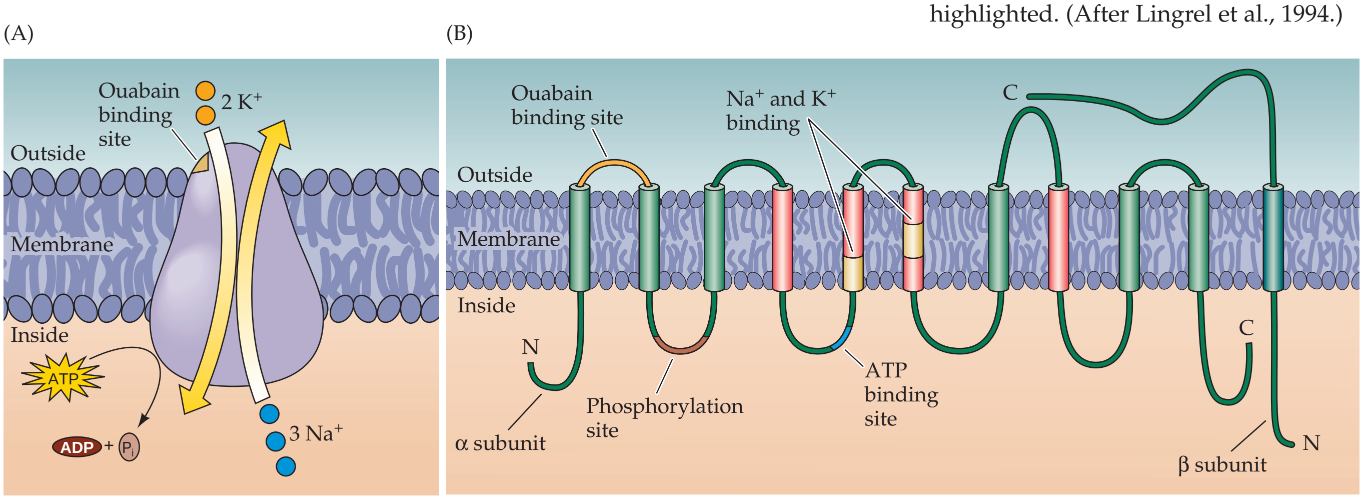


small unmyelinated axons produces a substantial hyperpolarization (Figure 4.12). During the period of stimulation, Na^+ enters through voltage-gated channels and accumulates within the axons. As the pump removes this extra Na^+, the resulting current generates a long-lasting hyperpolarization. Support for this interpretation comes from the observation that conditions that block the Na^+/K^+ pump—for example, treatment with ouabain, a plant glycoside that specifically inhibits the pump—prevent the hyperpolarization. The electrical contribution of the Na^+/K^+ pump is particularly significant in these small-diameter axons because their large surface-to-volume ratio causes intracellular Na^+ concentration to rise to higher levels than it would in other cells. Nonetheless, it is important to emphasize that, in most circumstances, the Na^+/K^+ pump plays no part in generating the action potential and has very little *direct* effect on the resting potential.

The Molecular Structure of the Na^+/K^+ Pump

These observations imply that the Na^+ and K^+ pump must exhibit several molecular properties: (1) It must bind both Na^+ and K^+; (2) it must possess sites that bind ATP and receive a phosphate group from this ATP; and (3) it must bind ouabain, the toxin that blocks this pump (Figure 4.13A). A variety of studies have now identified the aspects of the protein that account for these properties of the Na^+/K^+ pump. This pump is a large, integral membrane protein made up of at least two subunits, called α and β. The primary sequence shows that the α subunit spans the membrane 10 times, with most of the molecule found on the cytoplasmic side, whereas the β subunit spans the membrane once and is predominantly extracellular. Although a detailed account of the functional domains of the Na^+/K^+ pump is not yet available, some parts of the amino acid sequence have identified functions (Figure 4.13B). One intracellular domain of the protein is required for ATP binding

Figure 4.13 Molecular structure of the Na^+/K^+ pump. (A) General features of the pump. (B) The molecule spans the membrane 10 times. Amino acid residues thought to be important for binding of ATP, K^+, and ouabain are highlighted. (After Lingrel et al., 1994.)



and hydrolysis, and the amino acid phosphorylated by ATP has been identified. Another extracellular domain may represent the binding site for ouabain. However, the sites involved in the most critical function of the pump—the movement of Na^+ and K^+—have not yet been defined. Nonetheless, altering certain membrane-spanning domains (red in Figure 4.13B) impairs ion translocation; moreover, kinetic studies indicate that both ions bind to the pump at the same site. Because these ions move across the membrane, it is likely that this site traverses the plasma membrane; it is also likely that the site has a negative charge, since both Na^+ and K^+ are positively charged. The observation that removing negatively charged residues in a membrane-spanning domain of the protein (pale yellow in Figure 4.13B) greatly reduces Na^+ and K^+ binding provides at least a hint about the ion-translocating domain of the transporter molecule.

Summary

Ion transporters and channels have complementary functions. The primary purpose of transporters is to generate transmembrane concentration gradients, which are then exploited by ion channels to generate electrical signals. Ion channels are responsible for the voltage-dependent conductances of nerve cell membranes. The channels underlying the action potential are integral membrane proteins that open or close ion-selective pores in response to the membrane potential, allowing specific ions to diffuse across the membrane. The flow of ions through single open channels can be detected as tiny electrical currents, and the synchronous opening of many such channels generates the macroscopic currents that produce action potentials. Molecular studies show that such voltage-gated channels have highly conserved structures that are responsible for features such as ion permeation and voltage sensing, as well as the features that specify ion selectivity and toxin sensitivity. Other types of channels are sensitive to chemical signals, such as neurotransmitters or second messengers, or to heat or membrane deformation. A large number of ion channel genes create channels with a correspondingly wide range of functional characteristics, thus allowing different types of neurons to have a remarkable spectrum of electrical properties. Ion transporter proteins are quite different in both structure and function. The energy needed for ion movement against a concentration gradient (e.g., in maintaining the resting potential) is provided either by the hydrolysis of ATP or by the electrochemical gradient of co-transported ions. The Na^+/K^+ pump produces and maintains the transmembrane gradients of Na^+ and K^+, while other transporters are responsible for the electrochemical gradients for other physiologically important ions, such as Cl^-, Ca^{2+}, and H^+. Together, transporters and channels provide a reasonably comprehensive molecular explanation for the ability of neurons to generate electrical signals.

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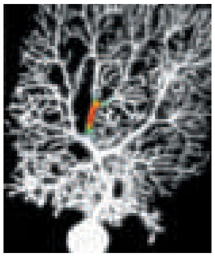
Chapter 5



Synaptic Transmission

Overview

The human brain contains at least 100 billion neurons, each with the ability to influence many other cells. Clearly, sophisticated and highly efficient mechanisms are needed to enable communication among this astronomical number of elements. Such communication is made possible by synapses, the functional contacts between neurons. Two different types of synapse—electrical and chemical—can be distinguished on the basis of their mechanism of transmission. At electrical synapses, current flows through gap junctions, which are specialized membrane channels that connect two cells. In contrast, chemical synapses enable cell-to-cell communication via the secretion of neurotransmitters; these chemical agents released by the presynaptic neurons produce secondary current flow in postsynaptic neurons by activating specific receptor molecules. The total number of neurotransmitters is not known, but is well over 100. Virtually all neurotransmitters undergo a similar cycle of use: synthesis and packaging into synaptic vesicles; release from the presynaptic cell; binding to postsynaptic receptors; and, finally, rapid removal and/or degradation. The secretion of neurotransmitters is triggered by the influx of Ca^{2+} through voltage-gated channels, which gives rise to a transient increase in Ca^{2+} concentration within the presynaptic terminal. The rise in Ca^{2+} concentration causes synaptic vesicles to fuse with the presynaptic plasma membrane and release their contents into the space between the pre- and postsynaptic cells. Although it is not yet understood exactly how Ca^{2+} triggers exocytosis, specific proteins on the surface of the synaptic vesicle and elsewhere in the presynaptic terminal mediate this process. Neurotransmitters evoke postsynaptic electrical responses by binding to members of a diverse group of neurotransmitter receptors. There are two major classes of receptors: those in which the receptor molecule is also an ion channel, and those in which the receptor and ion channel are separate molecules. These receptors give rise to electrical signals by transmitter-induced opening or closing of the ion channels. Whether the postsynaptic actions of a particular neurotransmitter are excitatory or inhibitory is determined by the ionic permeability of the ion channel affected by the transmitter, and by the concentration of permeant ions inside and outside the cell.

Electrical Synapses

Although there are many kinds of synapses within the human brain, they can be divided into two general classes: electrical synapses and chemical synapses. Although they are a distinct minority, electrical synapses are found in all nervous systems, permitting direct, passive flow of electrical current from one neuron to another.

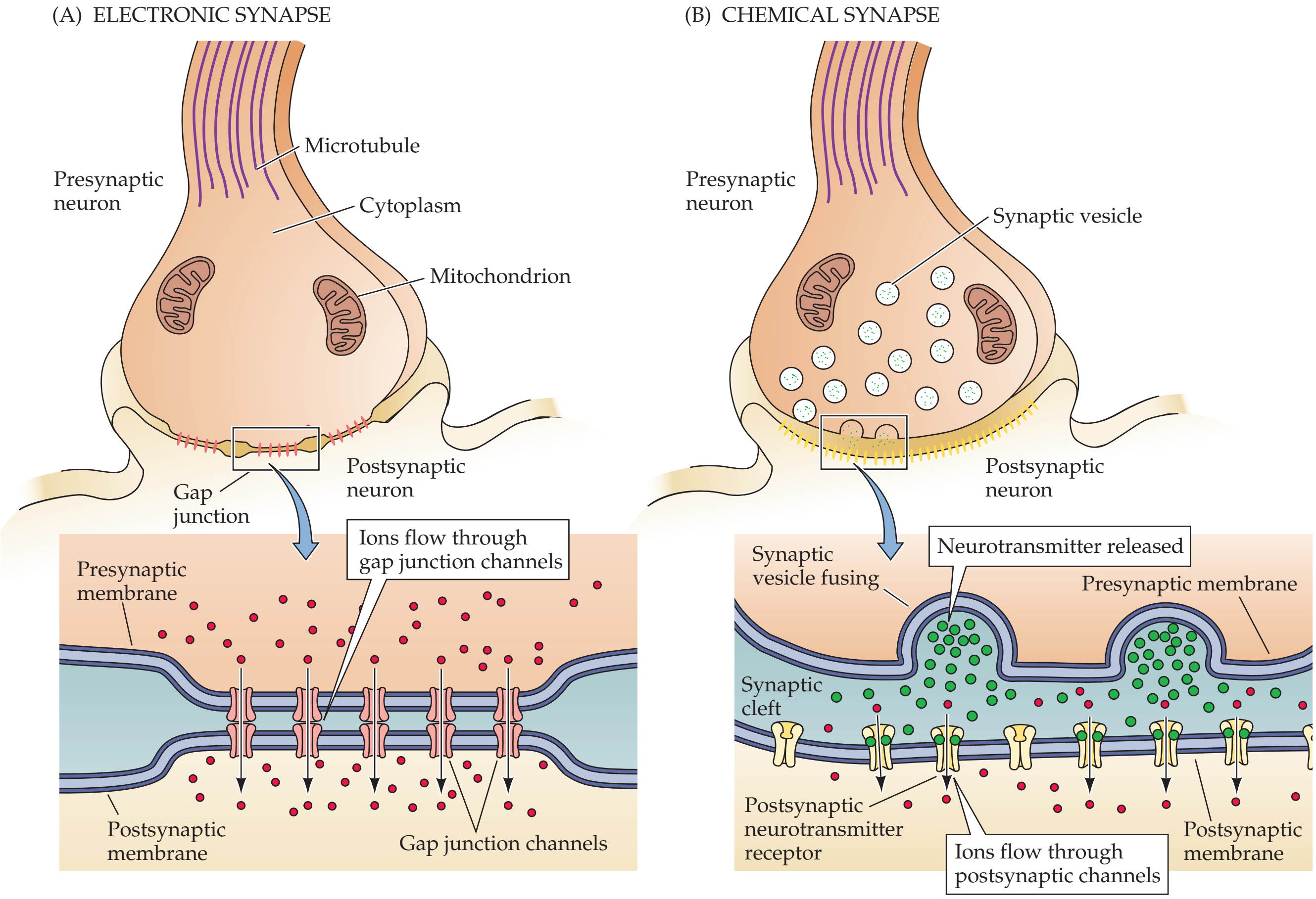

(A) ELECTRONIC SYNAPSE
Microtubule
Presynaptic neuron
Cytoplasm
Mitochondrion
Gap junction
Postsynaptic neuron
Ions flow through gap junction channels
Presynaptic membrane
Postsynaptic membrane
Gap junction channels
(B) CHEMICAL SYNAPSE
Presynaptic neuron
Synaptic vesicle
Postsynaptic neuron
Synaptic vesicle fusing
Neurotransmitter released
Presynaptic membrane
Synaptic cleft
Postsynaptic neurotransmitter receptor
Ions flow through postsynaptic channels
Postsynaptic membrane

Figure 5.1 Electrical and chemical synapses differ fundamentally in their transmission mechanisms. (A) At electrical synapses, gap junctions between pre- and postsynaptic membranes permit current to flow passively through intercellular channels (blowup). This current flow changes the postsynaptic membrane potential, initiating (or in some instances inhibiting) the generation of postsynaptic action potentials. (B) At chemical synapses, there is no intercellular continuity, and thus no direct flow of current from pre- to postsynaptic cell. Synaptic current flows across the postsynaptic membrane only in response to the secretion of neurotransmitters, which open or close postsynaptic ion channels after binding to receptor molecules (blowup).

The structure of an electrical synapse is shown schematically in Figure 5.1A. The "upstream" neuron, which is the source of current, is called the **presynaptic** element, and the "downstream" neuron into which this current flows is termed **postsynaptic**. The membranes of the two communicating neurons come extremely close at the synapse and are actually linked together by an intercellular specialization called a **gap junction**. Gap junctions contain precisely aligned, paired channels in the membrane of the pre- and postsynaptic neurons, such that each channel pair forms a pore (see Figure 5.2A). The pore of a gap junction channel is much larger than the pores of the voltage-gated ion channels described in the previous chapter. As a result, a variety of substances can simply diffuse between the cytoplasm of the pre- and postsynaptic neurons. In addition to ions, substances that diffuse through gap junction pores include molecules with molecular weights as great as several hundred daltons. This permits ATP and other important intracellular metabolites, such as second messengers (see Chapter 7), to be transferred between neurons.

Electrical synapses thus work by allowing ionic current to flow passively through the gap junction pores from one neuron to another. The usual source of this current is the potential difference generated locally by the action potential (see Chapter 3). This arrangement has a number of interesting consequences. One is that transmission can be bidirectional; that is, current can flow in either direction across the gap junction, depending on which member of the coupled pair is invaded by an action potential (although some types of gap junctions have special features that render their transmission unidirectional). Another important feature of the electrical synapse is that transmission is extraordinarily fast: because passive current flow across the gap junction is virtually instantaneous, communication can occur without the delay that is characteristic of chemical synapses.

These features are apparent in the operation of the first electrical synapse to be discovered, which resides in the crayfish nervous system. A postsynaptic electrical signal is observed at this synapse within a fraction of a millisecond after the generation of a presynaptic action potential (Figure 5.2). In fact, at least part of this brief synaptic delay is caused by propagation of the action potential into the presynaptic terminal, so that there may be essentially no delay at all in the transmission of electrical signals across the synapse. Such synapses interconnect many of the neurons within the circuit that allows the crayfish to escape from its predators, thus minimizing the time between the presence of a threatening stimulus and a potentially life-saving motor response.

A more general purpose of electrical synapses is to synchronize electrical activity among populations of neurons. For example, the brainstem neurons that generate rhythmic electrical activity underlying breathing are synchronized by electrical synapses, as are populations of interneurons in the cerebral cortex, thalamus, cerebellum, and other brain regions. Electrical transmission between certain hormone-secreting neurons within the mammalian hypothalamus ensures that all cells fire action potentials at about the same time, thus facilitating a burst of hormone secretion into the circulation. The fact that gap junction pores are large enough to allow molecules such as ATP and second messengers to diffuse intercellularly also permits electrical synapses to coordinate the intracellular signaling and metabolism of coupled cells. This property may be particularly important for glial cells, which form large intracellular signaling networks via their gap junctions.

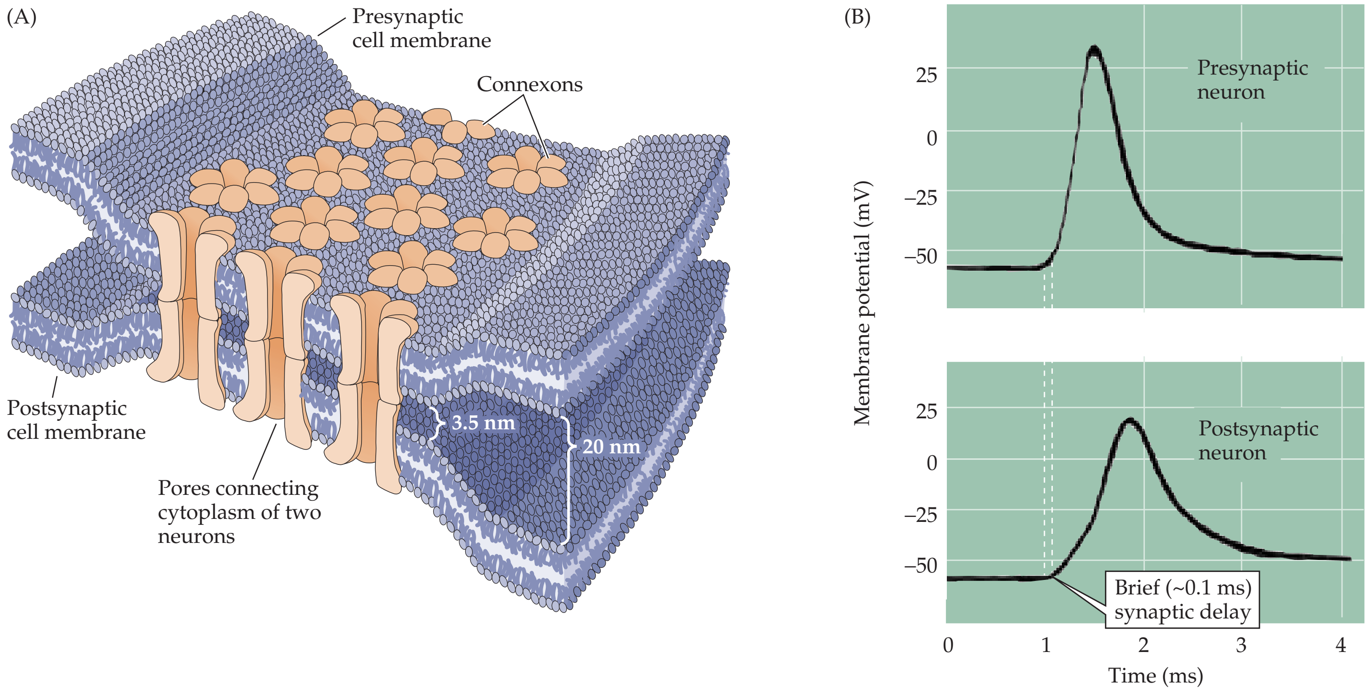

(A)
Presynaptic cell membrane
Connexons
Postsynaptic cell membrane
Pores connecting cytoplasm of two neurons
3.5 nm
20 nm
(B)
Membrane potential (mV)
25
0
–25
–50
Presynaptic neuron
25
0
–25
–50
Postsynaptic neuron
Brief (~0.1 ms) synaptic delay
0
1
2
3
4
Time (ms)

Figure 5.2 Structure and function of gap junctions at electrical synapses. (A) Gap junctions consist of hexameric complexes formed by the coming together of subunits called connexons, which are present in both the pre- and postsynaptic membranes. The pores of the channels connect to one another, creating electrical continuity between the two cells. (B) Rapid transmission of signals at an electrical synapse in the crayfish. An action potential in the presynaptic neuron causes the postsynaptic neuron to be depolarized within a fraction of a millisecond. (B after Furshpan and Potter, 1959.)

Signal Transmission at Chemical Synapses

The general structure of a chemical synapse is shown schematically in Figure 5.1B. The space between the pre- and postsynaptic neurons is substantially greater at chemical synapses than at electrical synapses and is called the **synaptic cleft**. However, the key feature of all chemical synapses is the presence of small, membrane-bounded organelles called **synaptic vesicles** within the presynaptic terminal. These spherical organelles are filled with one or more **neurotransmitters**, the chemical signals secreted from the presynaptic neuron, and it is these chemical agents acting as messengers between the communicating neurons that gives this type of synapse its name.

Transmission at chemical synapses is based on the elaborate sequence of events depicted in Figure 5.3. The process is initiated when an action potential invades the terminal of the presynaptic neuron. The change in membrane potential caused by the arrival of the action potential leads to the opening of voltage-gated calcium channels in the presynaptic membrane. Because of the steep concentration gradient of Ca^{2+} across the presynaptic membrane (the external Ca^{2+} concentration is approximately 10^{-3} *M*, whereas the internal Ca^{2+} concentration is approximately 10^{-7} *M*), the opening of these channels causes a rapid influx of Ca^{2+} into the presynaptic terminal, with the result that the Ca^{2+} concentration of the cytoplasm in the terminal transiently rises to a much higher value. Elevation of the presynaptic Ca^{2+} concentration, in turn, allows synaptic vesicles to fuse with the plasma membrane of the presynaptic neuron. The Ca^{2+}-dependent fusion of synaptic vesicles with the terminal membrane causes their contents, most importantly neurotransmitters, to be released into the synaptic cleft.

Following exocytosis, transmitters diffuse across the synaptic cleft and bind to specific receptors on the membrane of the postsynaptic neuron. The binding of neurotransmitter to the receptors causes channels in the postsynaptic membrane to open (or sometimes to close), thus changing the ability of ions to flow into (or out of) the postsynaptic cells. The resulting neurotransmitter-induced current flow alters the conductance and (usually) the membrane potential of the postsynaptic neuron, increasing or decreasing the probability that the neuron will fire an action potential. In this way, information is transmitted from one neuron to another.

Properties of Neurotransmitters

The notion that electrical information can be transferred from one neuron to the next by means of chemical signaling was the subject of intense debate through the first half of the twentieth century. A key experiment that supported this idea was performed in 1926 by German physiologist Otto Loewi. Acting on an idea that allegedly came to him in the middle of the night, Loewi proved that electrical stimulation of the vagus nerve slows the heartbeat by releasing a chemical signal. He isolated and perfused the hearts of two frogs, monitoring the rates at which they were beating (Figure 5.4). His experiment collected the perfusate flowing through the stimulated heart and transferred this solution to the second heart. When the vagus nerve to the first heart was stimulated, the beat of this heart slowed. Remarkably, even though the vagus nerve of the second heart had not been stimulated, its beat also slowed when exposed to the perfusate from the first heart. This result showed that the vagus nerve regulates the heart rate by releasing a chemical that accumulates in the perfusate. Originally referred to as "vagus substance," the agent was later shown to be **acetylcholine** (**ACh**). ACh is now known to be a neurotransmitter that acts not only in the heart but at a vari-

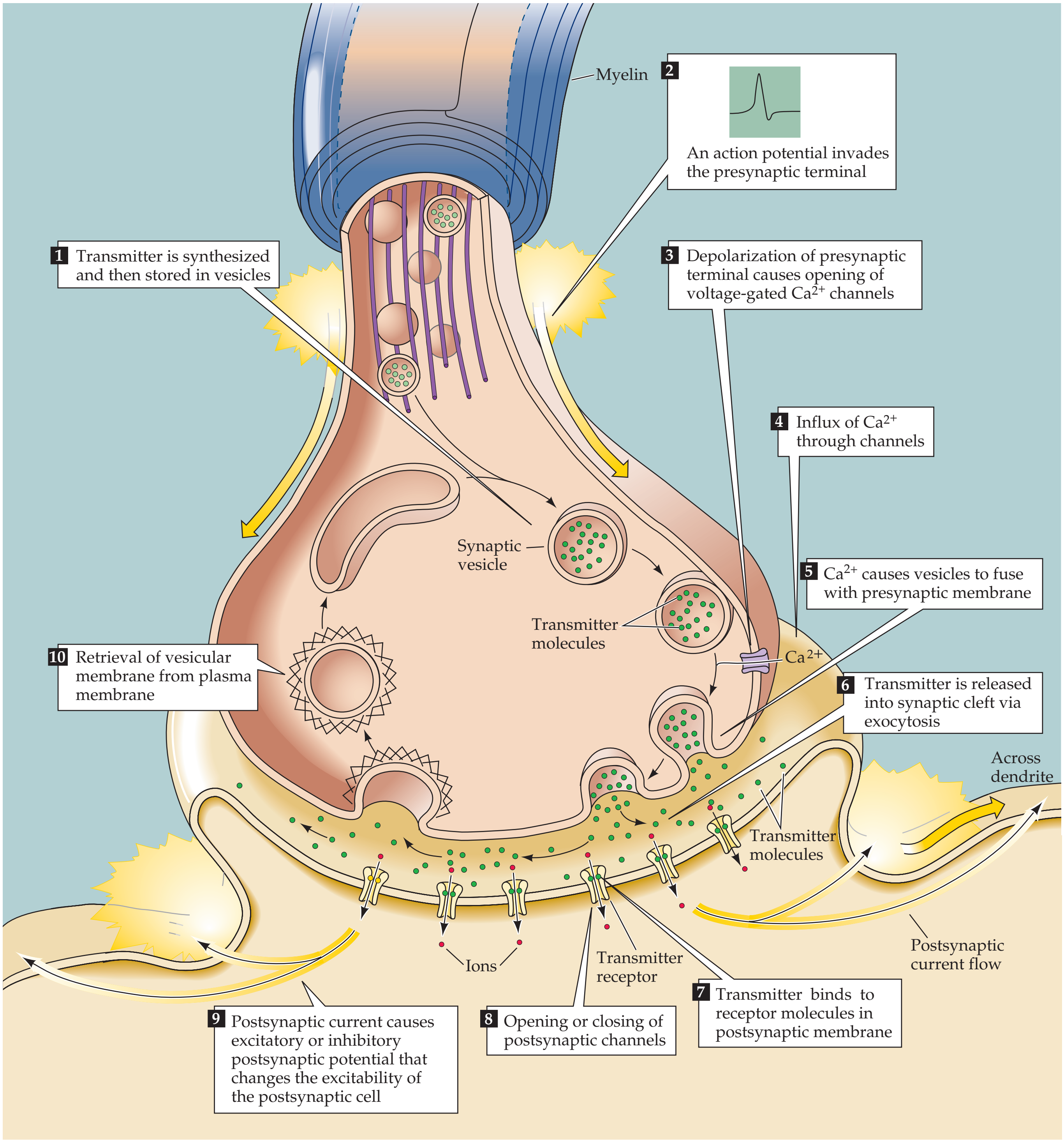

Myelin
2 An action potential invades the presynaptic terminal
1 Transmitter is synthesized and then stored in vesicles
3 Depolarization of presynaptic terminal causes opening of voltage-gated Ca^{2+} channels
4 Influx of Ca^{2+} through channels
Synaptic vesicle
5 Ca^{2+} causes vesicles to fuse with presynaptic membrane
Transmitter molecules
Ca^{2+}
10 Retrieval of vesicular membrane from plasma membrane
6 Transmitter is released into synaptic cleft via exocytosis
Across dendrite
Transmitter molecules
Postsynaptic current flow
Ions
Transmitter receptor
7 Transmitter binds to receptor molecules in postsynaptic membrane
8 Opening or closing of postsynaptic channels
9 Postsynaptic current causes excitatory or inhibitory postsynaptic potential that changes the excitability of the postsynaptic cell

Figure 5.3 Sequence of events involved in transmission at a typical chemical synapse.

ety of postsynaptic targets in the central and peripheral nervous systems, preeminently at the neuromuscular junction of striated muscles and in the visceral motor system (see Chapters 6 and 20).

Over the years, a number of formal criteria have emerged that definitively identify a substance as a neurotransmitter (Box A). These have led to the identification of more than 100 different neurotransmitters, which can be

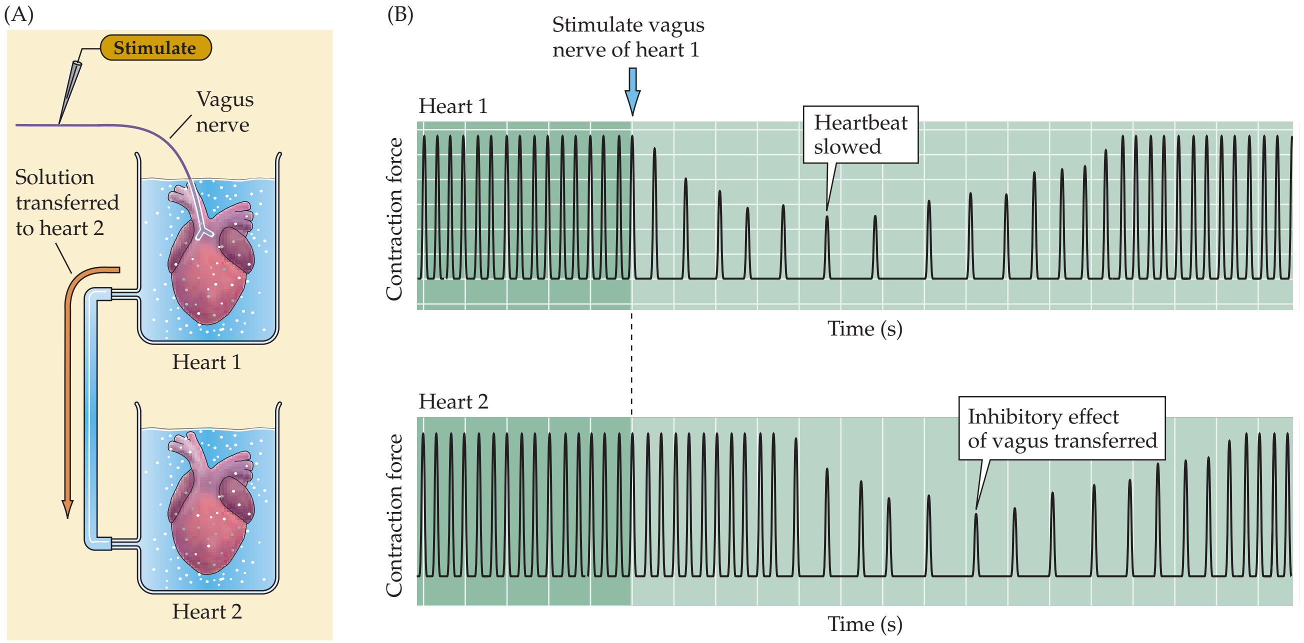


Figure 5.4 Loewi's experiment demonstrating chemical neurotransmission. (A) Diagram of experimental setup. (B) Where the vagus nerve of an isolated frog's heart was stimulated, the heart rate decreased (upper panel). If the perfusion fluid from the stimulated heart was transferred to a second heart, its rate decreased as well (lower panel).

classified into two broad categories: small-molecule neurotransmitters and neuropeptides (Chapter 6). Having more than one transmitter diversifies the physiological repertoire of synapses. Multiple neurotransmitters can produce different types of responses on individual postsynaptic cells. For example, a neuron can be excited by one type of neurotransmitter and inhibited by another type of neurotransmitter. The speed of postsynaptic responses produced by different transmitters also differs, allowing control of electrical signaling over different time scales. In general, small-molecule neurotransmitters mediate rapid synaptic actions, whereas neuropeptides tend to modulate slower, ongoing synaptic functions.

Until relatively recently, it was believed that a given neuron produced only a single type of neurotransmitter. It is now clear, however, that many types of neurons synthesize and release two or more different neurotransmitters. When more than one transmitter is present within a nerve terminal, the molecules are called **co-transmitters**. Because different types of transmitters can be packaged in different populations of synaptic vesicles, co-transmitters need not be released simultaneously. When peptide and small-molecule neurotransmitters act as co-transmitters at the same synapse, they are differentially released according to the pattern of synaptic activity: low-frequency activity often releases only small neurotransmitters, whereas high-frequency activity is required to release neuropeptides from the same presynaptic terminals. As a result, the chemical signaling properties of such synapses change according to the rate of activity.

Effective synaptic transmission requires close control of the concentration of neurotransmitters within the synaptic cleft. Neurons have therefore developed a sophisticated ability to regulate the synthesis, packaging, release, and

Box A
Criteria That Define a Neurotransmitter

Three primary criteria have been used to confirm that a molecule acts as a neurotransmitter at a given chemical synapse.

1. *The substance must be present within the presynaptic neuron*. Clearly, a chemical cannot be secreted from a presynaptic neuron unless it is present there. Because elaborate biochemical pathways are required to produce neurotransmitters, showing that the enzymes and precursors required to synthesize the substance are present in presynaptic neurons provides additional evidence that the substance is used as a transmitter. Note, however, that since the transmitters glutamate, glycine, and aspartate are also needed for protein synthesis and other metabolic reactions in all neurons, their presence is *not* sufficient evidence to establish them as neurotransmitters.

2. *The substance must be released in response to presynaptic depolarization, and the release must be Ca^{2+}-dependent*. Another essential criterion for identifying a neurotransmitter is to demonstrate that it is released from the presynaptic neuron in response to presynaptic electrical activity, and that this release requires Ca^{2+} influx into the presynaptic terminal. Meeting this criterion is technically challenging, not only because it may be difficult to selectively stimulate the presynaptic neurons, but also because enzymes and transporters efficiently remove the secreted neurotransmitters.

3. *Specific receptors for the substance must be present on the postsynaptic cell*. A neurotransmitter cannot act on its target unless specific receptors for the transmitter are present in the postsynaptic membrane. One way to demonstrate receptors is to show that application of exogenous transmitter mimics the postsynaptic effect of presynaptic stimulation. A more rigorous demonstration is to show that agonists and antagonists that alter the normal postsynaptic response have the same effect when the substance in question is applied exogenously. High-resolution histological methods can also be used to show that specific receptors are present in the postsynaptic membrane (by detection of radioactively labeled receptor antibodies, for example).

Fulfilling these criteria establishes unambiguously that a substance is used as a transmitter at a given synapse. Practical difficulties, however, have prevented these standards from being applied at many types of synapses. It is for this reason that so many substances must be referred to as "putative" neurotransmitters.

Demonstrating the identity of a neurotransmitter at a synapse requires showing (1) its presence, (2) its release, and (3) the postsynaptic presence of specific receptors.

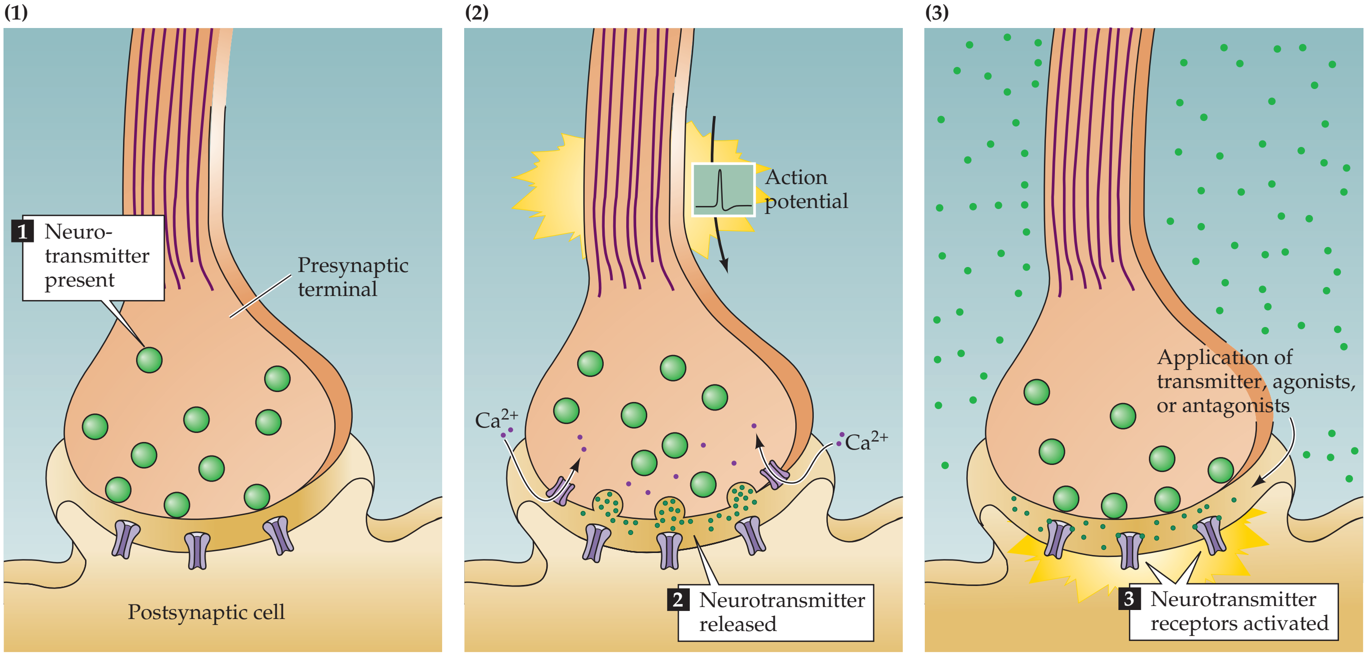
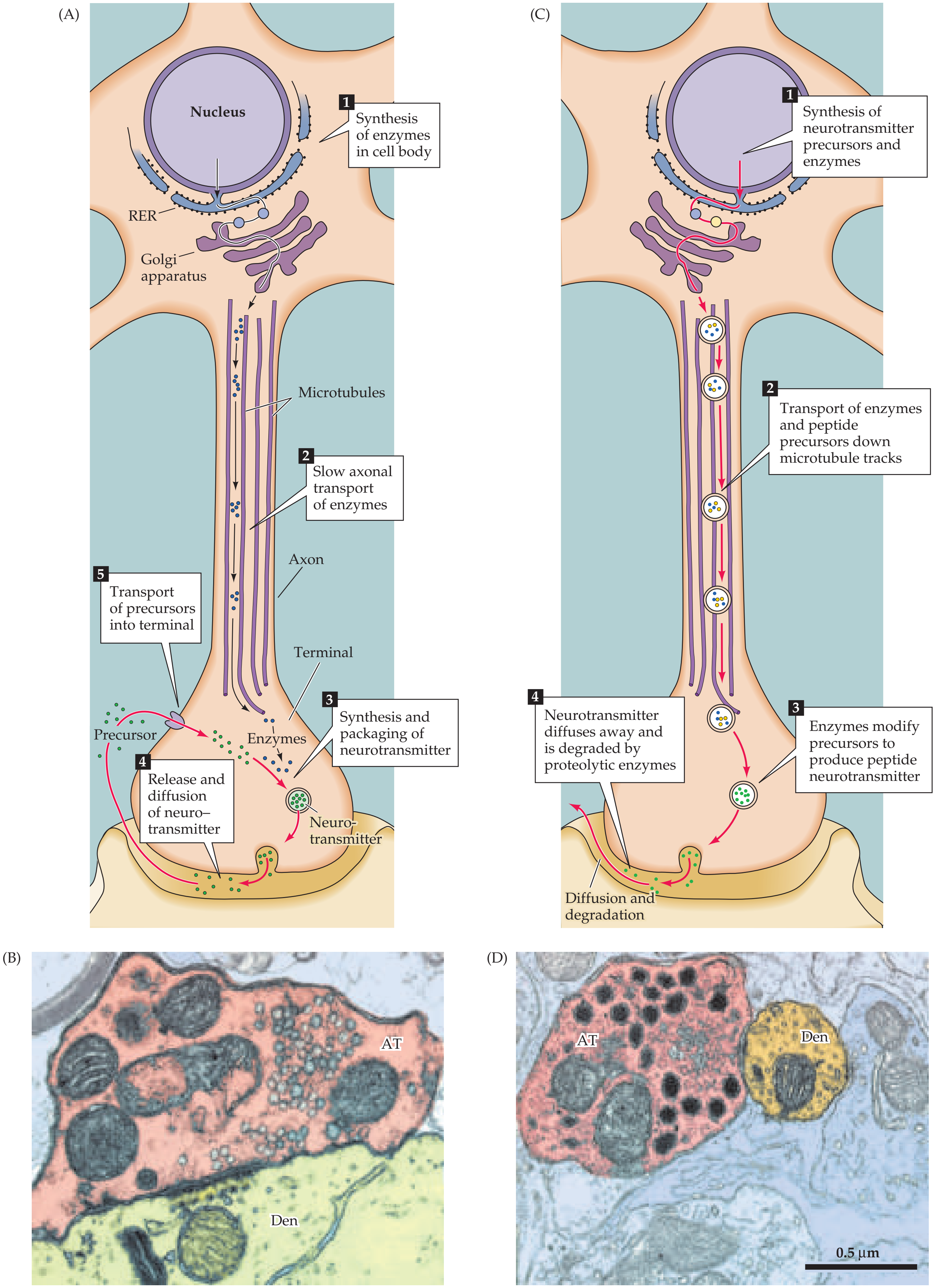

(1)
1 Neurotransmitter present
Presynaptic terminal
Postsynaptic cell
(2)
Action potential
Ca2+
Ca2+
2 Neurotransmitter released
(3)
Application of transmitter, agonists, or antagonists
3 Neurotransmitter receptors activated

Figure 5.5 Metabolism of small-molecule and peptide transmitters. (A) Small-molecule neurotransmitters are synthesized at nerve terminals. The enzymes necessary for neurotransmitter synthesis are made in the cell body of the presynaptic cell (1) and are transported down the axon by slow axonal transport (2). Precursors are taken up into the terminals by specific transporters, and neurotransmitter synthesis and packaging take place within the nerve endings (3). After vesicle fusion and release (4), the neurotransmitter may be enzymatically degraded. The reuptake of the neurotransmitter (or its metabolites) starts another cycle of synthesis, packaging, release, and removal (5). (B) Small clear-core vesicles at a synapse between an axon terminal (AT) and a dendritic spine (Den) in the central nervous system. Such vesicles typically contain small-molecule neurotransmitters. (C) Peptide neurotransmitters, as well as the enzymes that modify their precursors, are synthesized in the cell body (1). Enzymes and propeptides are packaged into vesicles in the Golgi apparatus. During fast axonal transport of these vesicles to the nerve terminals (2), the enzymes modify the propeptides to produce one or more neurotransmitter peptides (3). After vesicle fusion and exocytosis, the peptides diffuse away and are degraded by proteolytic enzymes (4). (D) Large dense-core vesicles in a central axon terminal (AT) synapsing onto a dendrite (Den). Such vesicles typically contain neuropeptides or, in some cases, biogenic amines. (B and D from Peters, Palay, and Webster, 1991.) ▶

degradation (or removal) of neurotransmitters to achieve the desired levels of transmitter molecules. The synthesis of small-molecule neurotransmitters occurs locally within presynaptic terminals (Figure 5.5A). The enzymes needed to synthesize these transmitters are produced in the neuronal cell body and transported to the nerve terminal cytoplasm at 0.5–5 millimeters a day by a mechanism called **slow axonal transport**. The precursor molecules required to make new molecules of neurotransmitter are usually taken into the nerve terminal by transporters found in the plasma membrane of the terminal. The enzymes synthesize neurotransmitters in the cytoplasm of the presynaptic terminal and the transmitters are then loaded into synaptic vesicles via transporters in the vesicular membrane (see Chapter 4). For some small-molecule neurotransmitters, the final steps of synthesis occur inside the synaptic vesicles. Most small-molecule neurotransmitters are packaged in vesicles 40 to 60 nm in diameter, the centers of which appear clear in electron micrographs; accordingly, these vesicles are referred to as **small clear-core vesicles** (Figure 5.5B). Neuropeptides are synthesized in the cell body of a neuron, meaning that the peptide is produced a long distance away from its site of secretion (Figure 5.5C). To solve this problem, peptide-filled vesicles are transported along an axon and down to the synaptic terminal via **fast axonal transport.** This process carries vesicles at rates up to 400 mm/day along cytoskeletal elements called microtubules (in contrast to the slow axonal transport of the enzymes that synthesize small-molecule transmitters). Microtubules are long, cylindrical filaments, 25 nm in diameter, present throughout neurons and other cells. Peptide-containing vesicles are moved along these microtubule "tracks" by ATP-requiring "motor" proteins such as kinesin. Neuropeptides are packaged into synaptic vesicles that range from 90 to 250 nm in diameter. These vesicles are electron-dense in electron micrographs—hence they are referred to as **large dense-core vesicles** (Figure 5.5D).

After a neurotransmitter has been secreted into the synaptic cleft, it must be removed to enable the postsynaptic cell to engage in another cycle of syn-


(A)
Nucleus
1
Synthesis of enzymes in cell body
RER
Golgi apparatus
Microtubules
2
Slow axonal transport of enzymes
Axon
5
Transport of precursors into terminal
Terminal
Precursor
Enzymes
3
Synthesis and packaging of neurotransmitter
4
Release and diffusion of neuro–transmitter
Neuro-transmitter
(C)
1
Synthesis of neurotransmitter precursors and enzymes
2
Transport of enzymes and peptide precursors down microtubule tracks
4
Neurotransmitter diffuses away and is degraded by proteolytic enzymes
3
Enzymes modify precursors to produce peptide neurotransmitter
Diffusion and degradation
(B)
AT
Den
(D)
AT
Den
0.5 μm

aptic transmission. The removal of neurotransmitters involves diffusion away from the postsynaptic receptors, in combination with reuptake into nerve terminals or surrounding glial cells, degradation by specific enzymes, or a combination of these mechanisms. Specific transporter proteins remove most small-molecule neurotransmitters (or their metabolites) from the synaptic cleft, ultimately delivering them back to the presynaptic terminal for reuse.

Quantal Release of Neurotransmitters

Much of the evidence leading to the present understanding of chemical synaptic transmission was obtained from experiments examining the release of ACh at neuromuscular junctions. These synapses between spinal motor neurons and skeletal muscle cells are simple, large, and peripherally located, making them particularly amenable to experimental analysis. Such synapses occur at specializations called **end plates** because of the saucer-like appearance of the site on the muscle fiber where the presynaptic axon elaborates its terminals (Figure 5.6A). Most of the pioneering work on neuromuscular transmission was performed by Bernard Katz and his collaborators at University College London during the 1950s and 1960s, and Katz has been widely recognized for his remarkable contributions to understanding synaptic transmission. Though he worked primarily on the frog neuromuscular junction, numerous subsequent experiments have confirmed the applicability of his observations to transmission at chemical synapses throughout the nervous system.

When an intracellular microelectrode is used to record the membrane potential of a muscle cell, an action potential in the presynaptic motor neuron can be seen to elicit a transient depolarization of the postsynaptic muscle fiber. This change in membrane potential, called an **end plate potential** (**EPP**), is normally large enough to bring the membrane potential of the muscle cell well above the threshold for producing a postsynaptic action potential (Figure 5.6B). The postsynaptic action potential triggered by the EPP causes the muscle fiber to contract. Unlike the case for electrical synapses, there is a pronounced delay between the time that the presynaptic motor neuron is stimulated and when the EPP occurs in the postsynaptic muscle cell. Such a delay is characteristic of all chemical synapses.

One of Katz's seminal findings, in studies carried out with Paul Fatt in 1951, was that spontaneous changes in muscle cell membrane potential occur even in the absence of stimulation of the presynaptic motor neuron (Figure 5.6C). These changes have the same shape as EPPs but are much

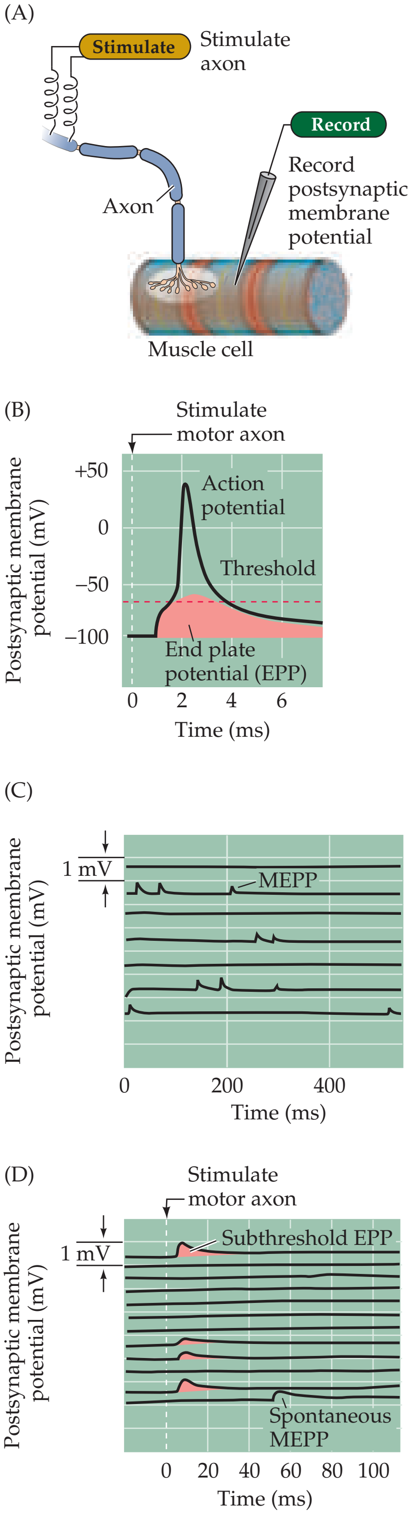


Figure 5.6 Synaptic transmission at the neuromuscular junction. (A) Experimental arrangement, typically using the muscle of a frog or rat. The axon of the motor neuron innervating the muscle fiber is stimulated with an extracellular electrode, while an intracellular microelectrode is inserted into the postsynaptic muscle cell to record its electrical responses. (B) End plate potentials (EPPs) evoked by stimulation of a motor neuron are normally above threshold and therefore produce an action potential in the postsynaptic muscle cell. (C) Spontaneous miniature EPPs (MEPPs) occur in the absence of presynaptic stimulation. (D) When the neuromuscular junction is bathed in a solution that has a low concentration of Ca^{2+}, stimulating the motor neuron evokes EPPs whose amplitudes are reduced to about the size of MEPPs. (After Fatt and Katz, 1952.)

smaller (typically less than 1 mV in amplitude, compared to an EPP of perhaps 40 or 50 mV). Both EPPs and these small, spontaneous events are sensitive to pharmacological agents that block postsynaptic acetylcholine receptors, such as curare (see Box B in Chapter 6). These and other parallels between EPPs and the spontaneously occurring depolarizations led Katz and his colleagues to call these spontaneous events **miniature end plate potentials**, or **MEPPs**.

The relationship between the full-blown end plate potential and MEPPs was clarified by careful analysis of the EPPs. The magnitude of the EPP provides a convenient electrical assay of neurotransmitter secretion from a motor neuron terminal; however, measuring it is complicated by the need to prevent muscle contraction from dislodging the microelectrode. The usual means of eliminating muscle contractions is either to lower Ca^{2+} concentration in the extracellular medium or to partially block the postsynaptic ACh receptors with the drug curare. As expected from the scheme illustrated in Figure 5.3, lowering the Ca^{2+} concentration reduces neurotransmitter secretion, thus reducing the magnitude of the EPP below the threshold for postsynaptic action potential production and allowing it to be measured more precisely. Under such conditions, stimulation of the motor neuron produces very small EPPs that fluctuate in amplitude from trial to trial (Figure 5.6D). These fluctuations give considerable insight into the mechanisms responsible for neurotransmitter release. In particular, the variable evoked response in low Ca^{2+} is now known to result from the release of unit amounts of ACh by the presynaptic nerve terminal. Indeed, the amplitude of the smallest evoked response is strikingly similar to the size of single MEPPs (compare Figure 5.6C and D). Further supporting this similarity, increments in the EPP response (Figure 5.7A) occur in units about the size of single MEPPs (Figure 5.7B). These "quantal" fluctuations in the amplitude of EPPs indicated to Katz and colleagues that EPPs are made up of individual units, each equivalent to a MEPP.

The idea that EPPs represent the simultaneous release of many MEPP-like units can be tested statistically. A method of statistical analysis based on the independent occurrence of unitary events (called Poisson statistics) predicts what the distribution of EPP amplitudes would look like during a large number of trials of motor neuron stimulation, under the assumption that EPPs are built up from unitary events like MEPPs (see Figure 5.7B). The distribution of EPP amplitudes determined experimentally was found to be just that expected if transmitter release from the motor neuron is indeed quantal (the red curve in Figure 5.7A). Such analyses confirmed the idea that release of acetylcholine does indeed occur in discrete packets, each equivalent to a MEPP. In short, a presynaptic action potential causes a postsynaptic EPP because it synchronizes the release of many transmitter quanta.

Release of Transmitters from Synaptic Vesicles

The discovery of the quantal release of packets of neurotransmitter immediately raised the question of how such quanta are formed and discharged into the synaptic cleft. At about the time Katz and his colleagues were using physiological methods to discover quantal release of neurotransmitter, electron microscopy revealed, for the first time, the presence of synaptic vesicles in presynaptic terminals. Putting these two discoveries together, Katz and others proposed that synaptic vesicles loaded with transmitter are the source of the quanta. Subsequent biochemical studies confirmed that synaptic vesi-

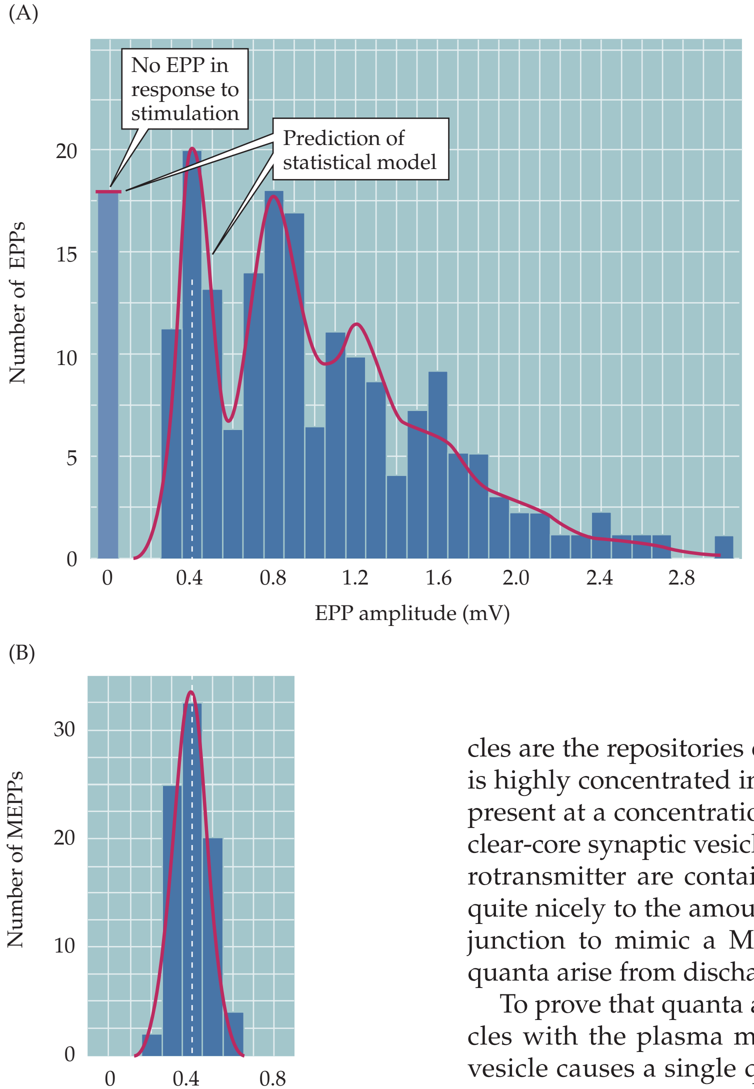


Figure 5.7 Quantized distribution of EPP amplitudes evoked in a low Ca^{2+} solution. Peaks of EPP amplitudes (A) tend to occur in integer multiples of the mean amplitude of MEPPs, whose amplitude distribution is shown in (B). The leftmost bar in the EPP amplitude distribution shows trials in which presynaptic stimulation failed to elicit an EPP in the muscle cell. The red curve indicates the prediction of a statistical model based on the assumption that the EPPs result from the independent release of multiple MEPP-like quanta. The observed match, including the predicted number of failures, supports this interpretation. (After Boyd and Martin, 1955.)

cles are the repositories of transmitters. These studies have shown that ACh is highly concentrated in the synaptic vesicles of motor neurons, where it is present at a concentration of about 100 m*M*. Given the diameter of a small, clear-core synaptic vesicle (~50 nm), approximately 10,000 molecules of neurotransmitter are contained in a single vesicle. This number corresponds quite nicely to the amount of ACh that must be applied to a neuromuscular junction to mimic a MEPP, providing further support for the idea that quanta arise from discharge of the contents of single synaptic vesicles.

To prove that quanta are caused by the fusion of individual synaptic vesicles with the plasma membrane, it is necessary to show that each fused vesicle causes a single quantal event to be recorded postsynaptically. This challenge was met in the late 1970s, when John Heuser, Tom Reese, and colleagues correlated measurements of vesicle fusion with the quantal content of EPPs at the neuromuscular junction. In their experiments, the number of vesicles that fused with the presynaptic plasma membrane was measured by electron microscopy in terminals that had been treated with a drug (4-aminopyridine, or 4-AP) that enhances the number of vesicle fusion events produced by single action potentials (Figure 5.8A). Parallel electrical measurements were made of the quantal content of the EPPs elicited in this way. A comparison of the number of synaptic vesicle fusions observed with the electron microscope and the number of quanta released at the synapse showed a good correlation between these two measures (Figure 5.8B). These results remain one of the strongest lines of support for the idea that a quantum of transmitter release is due to a synaptic vesicle fusing with the presynaptic membrane. Subsequent evidence, based on other means of measuring vesicle fusion, has left no doubt about the validity of this general interpretation of chemical synaptic transmission. Very recent work has identified structures within the presynaptic terminal that connect vesicles to the plasma membrane and may be involved in membrane fusion (Figure 5.8C).

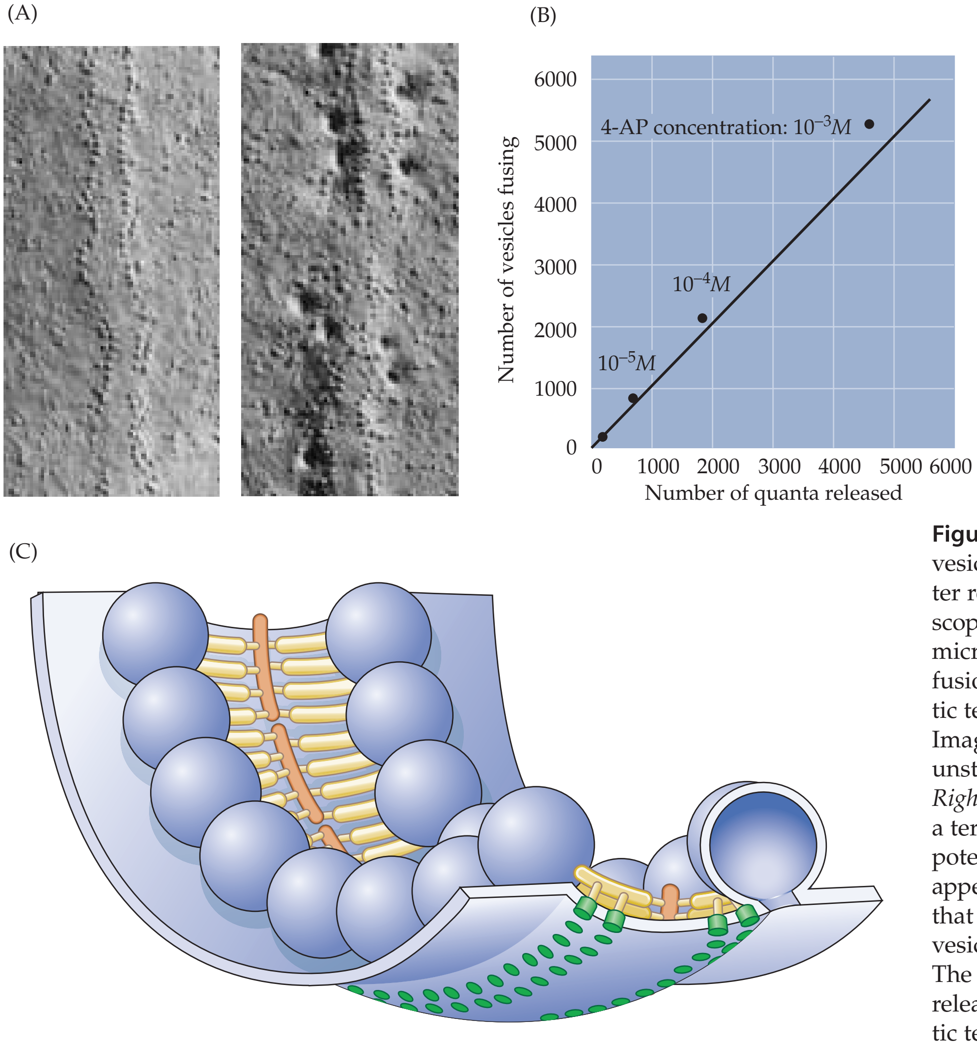


Figure 5.8 Relationship of synaptic vesicle exocytosis and quantal transmitter release. (A) A special electron microscopical technique called freeze-fracture microscopy was used to visualize the fusion of synaptic vesicles in presynaptic terminals of frog motor neurons. *Left:* Image of the plasma membrane of an unstimulated presynaptic terminal. *Right:* Image of the plasma membrane of a terminal stimulated by an action potential. Stimulation causes the appearance of dimple-like structures that represent the fusion of synaptic vesicles with the presynaptic membrane. The view is as if looking down on the release sites from outside the presynaptic terminal. (B) Comparison of the number of observed vesicle fusions to the number of quanta released by a presynaptic action potential. Transmitter release was varied by using a drug (4-AP) that affects the duration of the presynaptic action potential, thus changing the amount of calcium that enters during the action potential. The diagonal line is the 1:1 relationship expected if each vesicle that opened released a single quantum of transmitter. (C) Fine structure of vesicle fusion sites of frog presynaptic terminals. Synaptic vesicles are arranged in rows and are connected to each other and to the plasma membrane by a variety of proteinaceous structures (yellow). Green structures in the presynaptic membrane, corresponding to the rows of particles seen in (A), are thought to be Ca^{2+} channels. (A and B from Heuser et al., 1979; C after Harlow et al., 2001)

Local Recycling of Synaptic Vesicles

The fusion of synaptic vesicles causes new membrane to be added to the plasma membrane of the presynaptic terminal, but the addition is not permanent. Although a bout of exocytosis can dramatically increase the surface area of presynaptic terminals, this extra membrane is removed within a few minutes. Heuser and Reese performed another important set of experiments showing that the fused vesicle membrane is actually retrieved and taken back into the cytoplasm of the nerve terminal (a process called endocytosis). The experiments, again carried out at the frog neuromuscular junction, were based on filling the synaptic cleft with horseradish peroxidase (HRP), an enzyme that can be made to produce a dense reaction product that is visible in an electron microscope. Under appropriate experimental conditions, endocytosis could then be visualized by the uptake of HRP into the nerve terminal (Figure 5.9). To activate endocytosis, the presynaptic terminal was stimulated with a train of action potentials, and the subsequent fate of the HRP was followed by electron microscopy. Immediately follow-

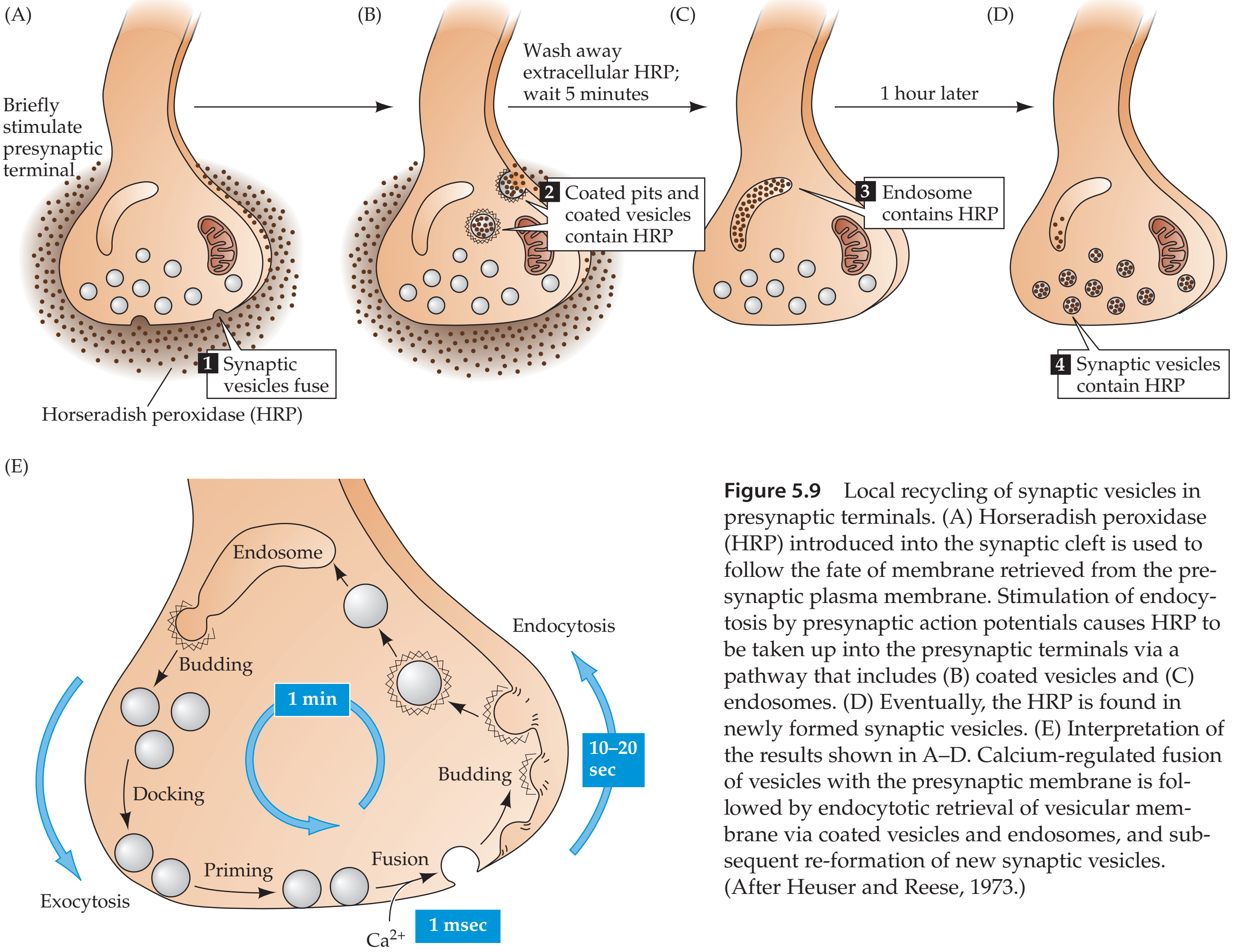

(A)
Briefly stimulate presynaptic terminal
1 Synaptic vesicles fuse
Horseradish peroxidase (HRP)
(B)
Wash away extracellular HRP; wait 5 minutes
2 Coated pits and coated vesicles contain HRP
(C)
1 hour later
3 Endosome contains HRP
(D)
4 Synaptic vesicles contain HRP
(E)
Endosome
Budding
Endocytosis
1 min
10–20 sec
Budding
Docking
Priming
Fusion
Exocytosis
Ca2+
1 msec

Figure 5.9 Local recycling of synaptic vesicles in presynaptic terminals. (A) Horseradish peroxidase (HRP) introduced into the synaptic cleft is used to follow the fate of membrane retrieved from the presynaptic plasma membrane. Stimulation of endocytosis by presynaptic action potentials causes HRP to be taken up into the presynaptic terminals via a pathway that includes (B) coated vesicles and (C) endosomes. (D) Eventually, the HRP is found in newly formed synaptic vesicles. (E) Interpretation of the results shown in A–D. Calcium-regulated fusion of vesicles with the presynaptic membrane is followed by endocytotic retrieval of vesicular membrane via coated vesicles and endosomes, and subsequent re-formation of new synaptic vesicles. (After Heuser and Reese, 1973.)

ing stimulation, the HRP was found within special endocytotic organelles called coated vesicles (Figure 5.9A,B). A few minutes later, however, the coated vesicles had disappeared and the HRP was found in a different organelle, the endosome (Figure 5.9C). Finally, within an hour after stimulating the terminal, the HRP reaction product appeared inside synaptic vesicles (Figure 5.9D).

These observations indicate that synaptic vesicle membrane is recycled within the presynaptic terminal via the sequence summarized in Figure 5.9E. In this process, called the **synaptic vesicle cycle**, the retrieved vesicular membrane passes through a number of intracellular compartments—such as coated vesicles and endosomes—and is eventually used to make new synaptic vesicles. After synaptic vesicles are re-formed, they are stored in a reserve pool within the cytoplasm until they need to participate again in neurotransmitter release. These vesicles are mobilized from the reserve pool, docked at the presynaptic plasma membrane, and primed to participate in exocytosis once again. More recent experiments, employing a fluorescent label rather than HRP, have determined the time course of synaptic vesicle recycling. These studies indicate that the entire vesicle cycle requires approximately 1 minute, with membrane budding during endocytosis requiring 10–20 seconds of this time. As can be seen from the 1-millisecond delay in transmission following excitation of the presynaptic terminal (see Figure 5.6B), membrane fusion during exocytosis is much more rapid than budding during endocytosis. Thus, all of the recycling steps interspersed between membrane budding and subsequent refusion of a vesicle are completed in less than a minute.

The precursors to synaptic vesicles *originally* are produced in the endoplasmic reticulum and Golgi apparatus in the neuronal cell body. Because of the long distance between the cell body and the presynaptic terminal in most neurons, transport of vesicles from the soma would not permit rapid replenishment of synaptic vesicles during continuous neural activity. Thus, local recycling is well suited to the peculiar anatomy of neurons, giving nerve terminals the means to provide a continual supply of synaptic vesicles. As might be expected, defects in synaptic vesicle recycling can cause severe neurological disorders, some of which are described in Box B.

The Role of Calcium in Transmitter Secretion

As was apparent in the experiments of Katz and others described in the preceding sections, lowering the concentration of Ca^{2+} outside a presynaptic motor nerve terminal reduces the size of the EPP (compare Figure 5.6B and D). Moreover, measurement of the number of transmitter quanta released under such conditions shows that the reason the EPP gets smaller is that lowering Ca^{2+} concentration decreases the number of vesicles that fuse with the plasma membrane of the terminal. An important insight into *how* Ca^{2+} regulates the fusion of synaptic vesicles was the discovery that presynaptic terminals have voltage-sensitive Ca^{2+} channels in their plasma membranes (see Chapter 4).

The first indication of presynaptic Ca^{2+} channels was provided by Katz and Ricardo Miledi. They observed that presynaptic terminals treated with tetrodotoxin (which blocks Na^+ channels; see Chapter 3) could still produce a peculiarly prolonged type of action potential. The explanation for this surprising finding was that current was still flowing through Ca^{2+} channels, substituting for the current ordinarily carried by the blocked Na^+ channels. Subsequent voltage clamp experiments, performed by Rodolfo Llinás and others at a giant presynaptic terminal of the squid (Figure 5.10A), confirmed

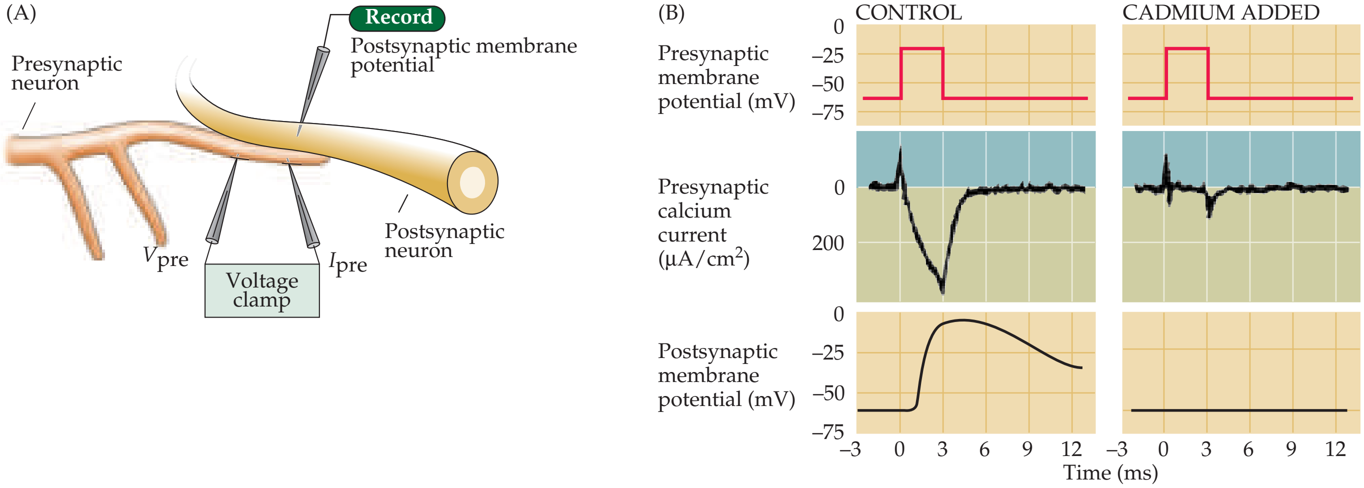


Figure 5.10 The entry of Ca^{2+} through the specific voltage-dependent calcium channels in the presynaptic terminals causes transmitter release. (A) Experimental setup using an extraordinarily large synapse in the squid. The voltage clamp method detects currents flowing across the presynaptic membrane when the membrane potential is depolarized. (B) Pharmacological agents that block currents flowing through Na^+ and K^+ channels reveal a remaining inward current flowing through Ca^{2+} channels. This influx of calcium triggers transmitter secretion, as indicated by a change in the postsynaptic membrane potential. Treatment of the same presynaptic terminal with cadmium, a calcium channel blocker, eliminates both the presynaptic calcium current and the postsynaptic response. (After Augustine and Eckert, 1984.)

Box B

Diseases That Affect the Presynaptic Terminal

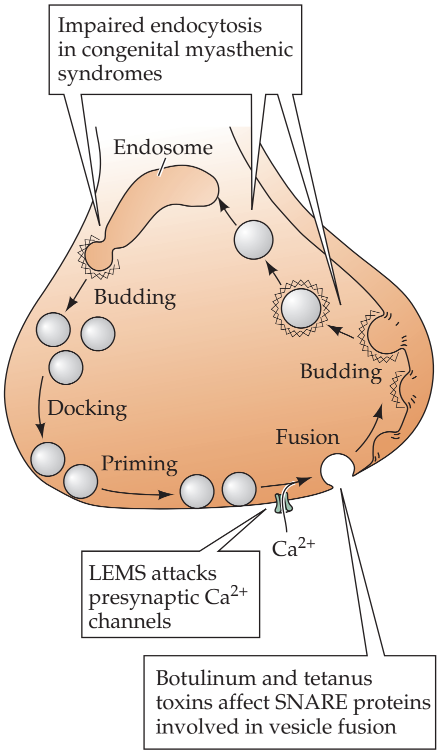
Various steps in the exocytosis and endocytosis of synaptic vesicles are targets of a number of rare but debilitating neurological diseases. Many of these are myasthenic syndromes, in which abnormal transmission at neuromuscular synapses leads to weakness and fatigability of skeletal muscles (see Box B in Chapter 7). One of the best-understood examples of such disorders is the Lambert-Eaton myasthenic syndrome (LEMS), an occasional complication in patients with certain kinds of cancers. Biopsies of muscle tissue removed from LEMS patients allow intracellular recordings identical to those shown in Figure 5.6. Such recordings have shown that when a motor neuron is stimulated, the number of quanta contained in individual EPPs is greatly reduced, although the amplitude of spontaneous MEPPs is normal. Thus, LEMS impairs evoked neurotransmitter release, but does not affect the size of individual quanta.

Several lines of evidence indicate that this reduction in neurotransmitter release is due to a loss of voltage-gated Ca^{2+} channels in the presynaptic terminal of motor neurons (see figure). Thus, the defect in neuromuscular transmission can be overcome by increasing the extracellular concentration of Ca^{2+}, and anatomical studies indicate a lower density of Ca^{2+} channel proteins in the presynaptic plasma membrane. The loss of presynaptic Ca^{2+} channels in LEMS apparently arises from a defect in the immune system. The blood of LEMS patients has a very high concentration of antibodies that bind to Ca^{2+} channels, and it seems likely that these antibodies are the primary cause of LEMS. For example, removal of Ca^{2+} channel antibodies from the blood of LEMS patients by plasma exchange reduces muscle weakness. Similarly, immunosuppressant drugs also can alleviate LEMS symptoms. Perhaps most telling, injecting these antibodies into experimental animals elicits muscle weakness and abnormal neuromuscular transmission. Why the immune system generates antibodies against Ca^{2+} channels is not clear. Most LEMS patients have small-cell carcinoma, a form of lung cancer that may somehow initiate the immune response to Ca^{2+} channels. Whatever the origin, the binding of antibodies to Ca^{2+} channels causes a reduction in Ca^{2+} channel currents. It is this antibody-induced defect in presynaptic Ca^{2+} entry that accounts for the muscle weakness associated with LEMS.

Congenital myasthenic syndromes are genetic disorders that also cause muscle weakness by affecting neuromuscular transmission. Some of these syndromes affect the acetylcholinesterase that degrades acetylcholine in the synaptic cleft, whereas others arise from autoimmune attack of acetylcholine receptors (see Box C in Chapter 6). However, a number of congenital myasthenic syndromes arise from defects in acetylcholine release due to altered synaptic vesicle traffic within the motor neuron terminal. Neuromuscular synapses in some of these patients have EPPs with reduced quantal content, a deficit that is especially prominent when the synapse is activated repeatedly. Electron microscopy shows that presynaptic motor nerve terminals have a greatly reduced number of synaptic vesicles. The defect in neurotransmitter release evidently results from an inadequate number of synaptic vesicles available for release during sustained presynaptic activity. The origins of this shortage of synaptic vesicles is not clear, but could result either from an impairment in endocytosis in the nerve terminal (see figure) or from a reduced supply of vesicles from the motor neuron cell body.

Still other patients suffering from familial infantile myasthenia appear to have neuromuscular weakness that arises from reductions in the size of individual quanta, rather than the number of quanta released. Motor nerve terminals from these patients have synaptic vesicles that are normal in number, but smaller in diameter. This finding suggests a different type of genetic lesion that somehow alters formation of new synaptic vesicles following endocytosis, thereby leading to less acetylcholine in each vesicle.

Another disorder of synaptic transmitter release results from poisoning by anaerobic *Clostridium* bacteria. This genus of microorganisms produces some


Impaired endocytosis in congenital myasthenic syndromes
Endosome
Budding
Budding
Docking
Fusion
Priming
Ca^{2+}
LEMS attacks presynaptic Ca^{2+} channels
Botulinum and tetanus toxins affect SNARE proteins involved in vesicle fusion

Presynaptic targets of several neurological disorders.

of the most potent toxins known, including several botulinum toxins and tetanus toxin. Both botulism and tetanus are potentially deadly disorders.

Botulism can occur by consuming food containing *Clostridium* bacteria or by infection of wounds with the spores of these ubiquitous organisms. In either case, the presence of the toxin can cause paralysis of peripheral neuromuscular synapses due to abolition of neurotransmitter release. This interference with neuromuscular transmission causes skeletal muscle weakness, in extreme cases producing respiratory failure due to paralysis of the diaphragm and other muscles required for breathing. Botulinum toxins also block synapses innervating the smooth muscles of several organs, giving rise to visceral motor dysfunction.

Tetanus typically results from the contamination of puncture wounds by *Clostridium* bacteria that produce tetanus toxin. In contrast to botulism, tetanus poisoning blocks the release of inhibitory transmitters from interneurons in the spinal cord. This effect causes a loss of synaptic inhibition on spinal motor neurons, producing hyperexcitation of skeletal muscle and tetanic contractions in affected muscles (hence the name of the disease).

Although their clinical consequences are dramatically different, clostridial toxins have a common mechanism of action (see figure). Tetanus toxin and botulinum toxins work by cleaving the SNARE proteins involved in fusion of synaptic vesicles with the presynaptic plasma membrane (see Box C). This proteolytic action presumably accounts for the block of transmitter release at the afflicted synapses. The different actions of these toxins on synaptic transmission at excitatory motor versus inhibitory synapses apparently results from the fact that these toxins are taken up by different types of neurons: Whereas the botulinum toxins are taken up by motor neurons, tetanus toxin is preferentially targeted to interneurons. The basis for this differential uptake of toxins is not known, but presumably arises from the presence of different types of toxin receptors on the two types of neurons.

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the presence of voltage-gated Ca^{2+} channels in the presynaptic terminal (Figure 5.10B). Such experiments showed that the amount of neurotransmitter released is very sensitive to the exact amount of Ca^{2+} that enters. Further, blockade of these Ca^{2+} channels with drugs also inhibits transmitter release (Figure 5.10B, right). These observations all confirm that the voltage-gated Ca^{2+} channels are directly involved in neurotransmission. Thus, presynaptic action potentials open voltage-gated Ca^{2+} channels, with a resulting influx of Ca^{2+}.

That Ca^{2+} entry into presynaptic terminals causes a rise in the concentration of Ca^{2+} within the terminal has been documented by microscopic imaging of terminals filled with Ca^{2+}-sensitive fluorescent dyes (Figure 5.11A). The consequences of the rise in presynaptic Ca^{2+} concentration for neurotransmitter release has been directly shown in two ways. First, microinjection of Ca^{2+} into presynaptic terminals triggers transmitter release in the absence of presynaptic action potentials (Figure 5.11B). Second, presynaptic microinjection of calcium chelators (chemicals that bind Ca^{2+} and keep its concentration buffered at low levels) prevents presynaptic action potentials from causing transmitter secretion (Figure 5.11C). These results prove beyond any doubt that a rise in presynaptic Ca^{2+} concentration is both necessary and sufficient for neurotransmitter release. Thus, as is the case for many other forms of neuronal signaling (see Chapter 7), Ca^{2+} serves as a second messenger during transmitter release.

While Ca^{2+} is a universal trigger for transmitter release, not all transmitters are released with the same speed. For example, while secretion of ACh

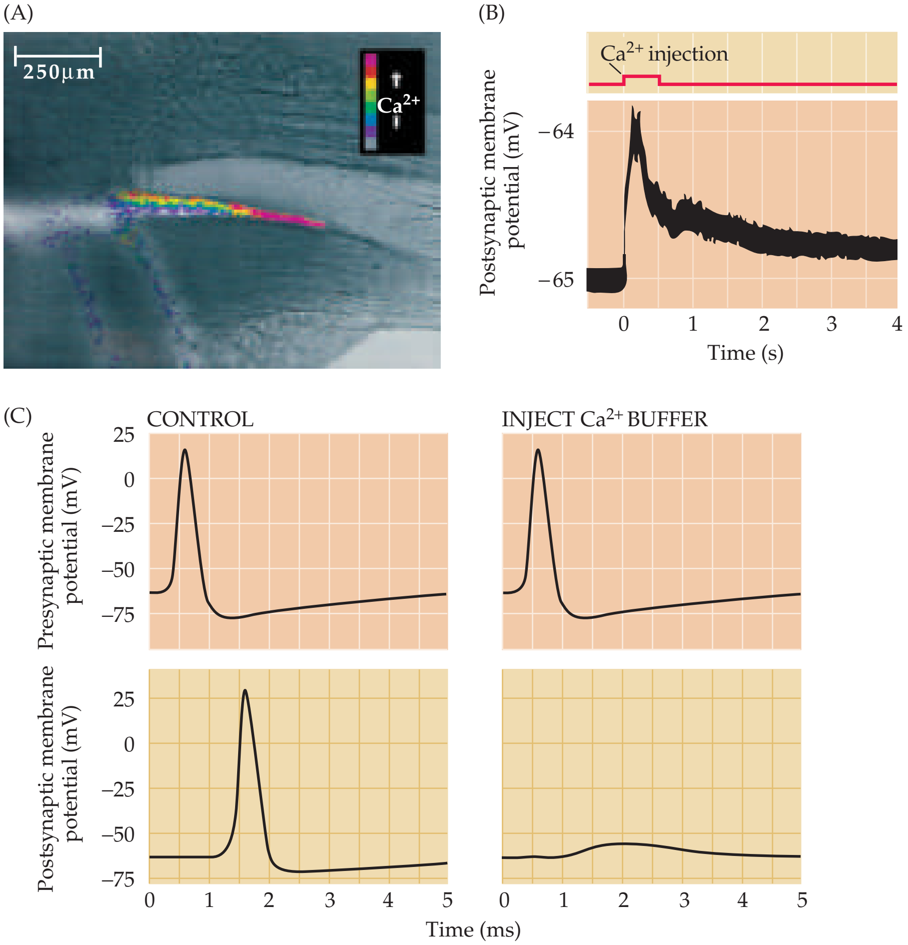


Figure 5.11 Evidence that a rise in presynaptic Ca^{2+} concentration triggers transmitter release from presynaptic terminals. (A) Fluorescence microscopy measurements of presynaptic Ca^{2+} concentration at the squid giant synapse (see Figure 5.8A). A train of presynaptic action potentials causes a rise in Ca^{2+} concentration, as revealed by a dye (called fura-2) that fluoresces more strongly when the Ca^{2+} concentration increases. (B) Microinjection of Ca^{2+} into a squid giant presynaptic terminal triggers transmitter release, measured as a depolarization of the postsynaptic membrane potential. (C) Microinjection of BAPTA, a Ca^{2+} chelator, into a squid giant presynaptic terminal prevents transmitter release. (A from Smith et al., 1993; B after Miledi, 1971; C after Adler et al., 1991.)

from motor neurons requires only a fraction of a millisecond (see Figure 5.6), release of neuropeptides require high-frequency bursts of action potentials for many seconds. These differences in the rate of release probably arise from differences in the spatial arrangement of vesicles relative to presynaptic Ca^{2+} channels. This perhaps is most evident in cases where small molecules and peptides serve as co-transmitters (Figure 5.12). Whereas the small, clear-core vesicles containing small-molecule transmitters are typically docked at the plasma membrane in advance of Ca^{2+} entry, large dense core vesicles containing peptide transmitters are farther away from the plasma membrane (see Figure 5.5D). At low firing frequencies, the concentration of Ca^{2+} may increase only locally at the presynaptic plasma membrane, in the vicinity of open Ca^{2+} channels, limiting release to small-molecule transmitters from the docked small, clear-core vesicles. Prolonged high-frequency stimulation increases the Ca^{2+} concentration throughout the presynaptic terminal, thereby inducing the slower release of neuropeptides.

Molecular Mechanisms of Transmitter Secretion

Precisely how an increase in presynaptic Ca^{2+} concentration goes on to trigger vesicle fusion and neurotransmitter release is not understood. However, many important clues have come from molecular studies that have identified and characterized the proteins found on synaptic vesicles and their binding

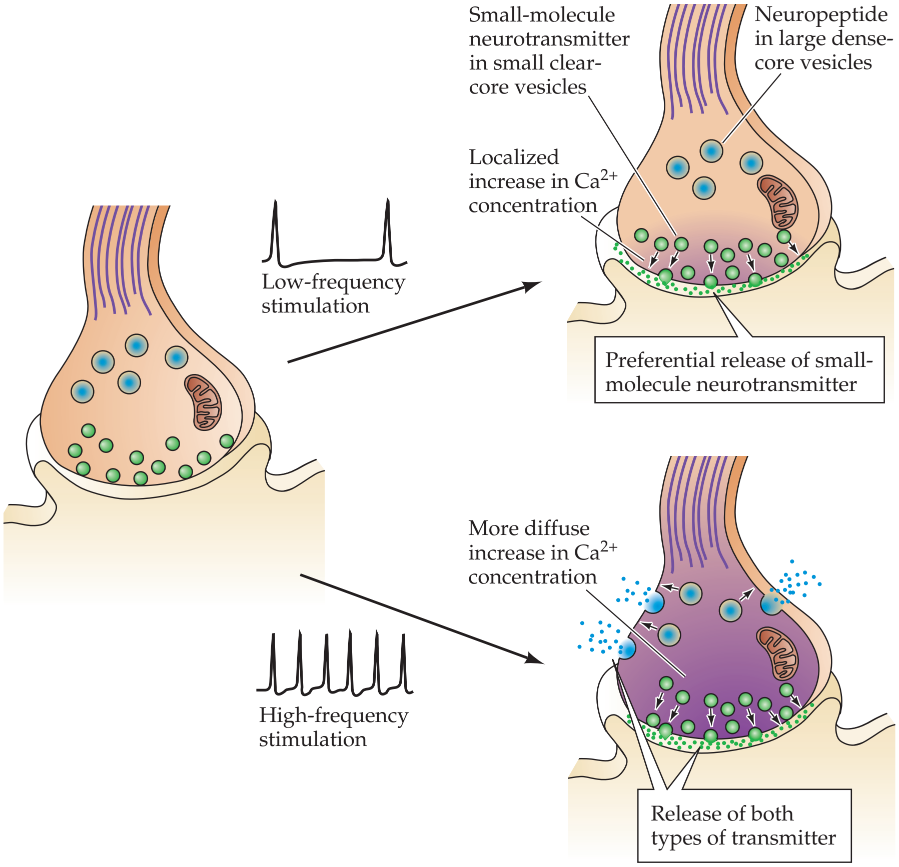

Small-molecule neurotransmitter in small clear-core vesicles
Neuropeptide in large dense-core vesicles
Localized increase in Ca2+ concentration
Low-frequency stimulation
Preferential release of small-molecule neurotransmitter
More diffuse increase in Ca2+ concentration
High-frequency stimulation
Release of both types of transmitter

Figure 5.12 Differential release of neuropeptide and small-molecule co-transmitters. Low-frequency stimulation preferentially raises the Ca^{2+} concentration close to the membrane, favoring the release of transmitter from small clear-core vesicles docked at presynaptic specializations. High-frequency stimulation leads to a more general increase in Ca^{2+}, causing the release of peptide neurotransmitters from large dense-core vesicles, as well as small-molecule neurotransmitters from small clear-core vesicles.

partners on the presynaptic plasma membrane and cytoplasm (Figure 5.13). Most, if not all, of these proteins act at one or more steps in the synaptic vesicle cycle. Although a complete molecular picture of neurotransmitter release is still lacking, the roles of several proteins involved in vesicle fusion have been deduced.

Several of the proteins important for neurotransmitter release are also involved in other types of membrane fusion events common to all cells. For example, two proteins originally found to be important for the fusion of vesicles with membranes of the Golgi apparatus, the ATPase **NSF** (*N*EM-*s*ensitive *f*usion protein) and **SNAPs** (*s*oluble *N*SF-*a*ttachment *p*roteins), are also involved in priming synaptic vesicles for fusion. These two proteins work by regulating the assembly of other proteins that are called **SNAREs** (*SNAP re*ceptors). One of these SNARE proteins, **synaptobrevin**, is in the membrane of synaptic vesicles, while two other SNARE proteins called **syntaxin** and **SNAP-25** are found primarily on the plasma membrane. These SNARE proteins can form a macromolecular complex that spans the two membranes, thus bringing them into close apposition (Figure 5.14A). Such an arrangement is well suited to promote the fusion of the two membranes, and several lines of evidence suggest that this is what actually occurs. One important observation is that toxins that cleave the SNARE proteins block neurotransmitter release (Box C). In addition, putting SNARE proteins into artificial lipid membranes and allowing these proteins to form complexes with each other causes the membranes to fuse. Many other proteins, such as

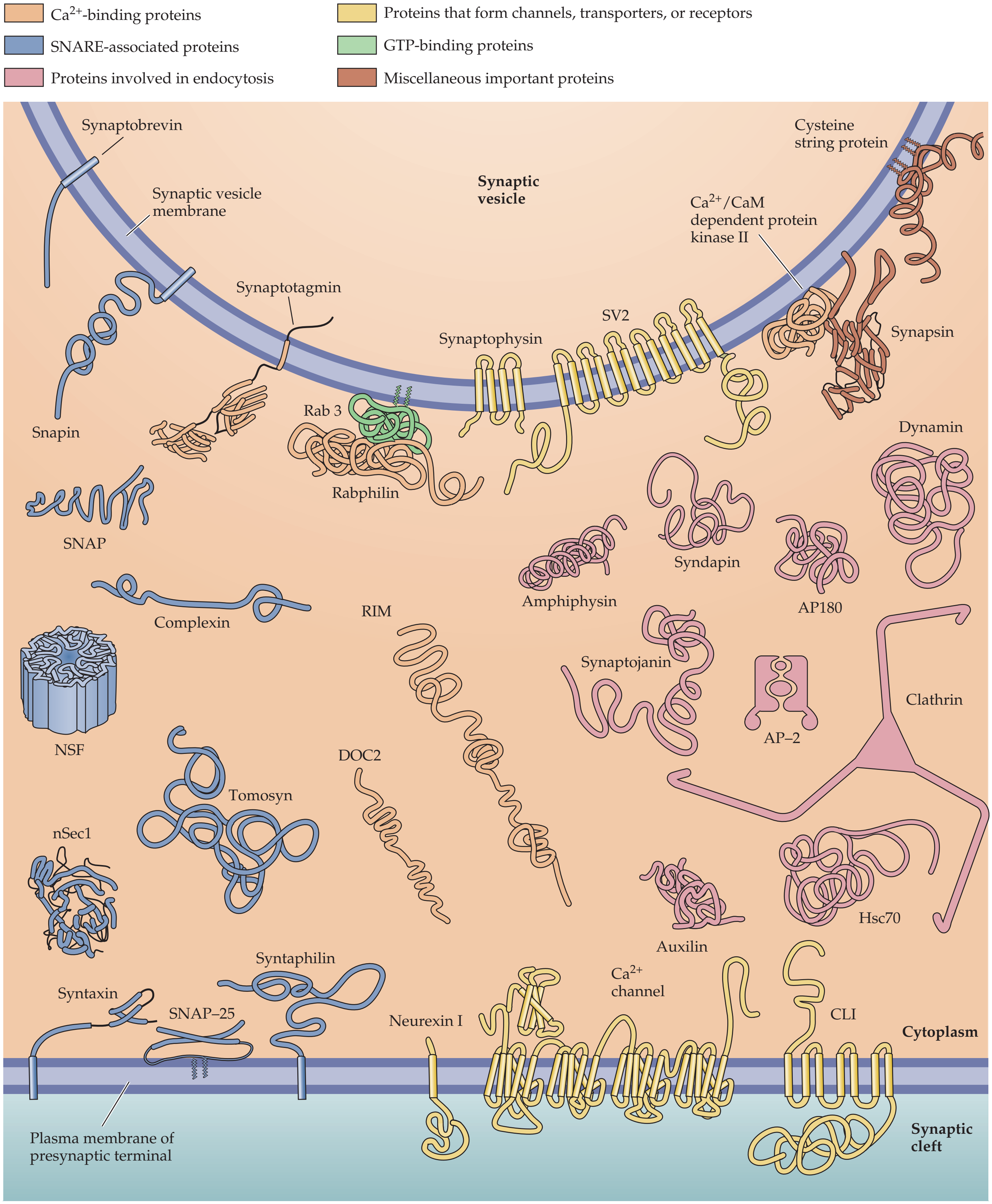

Ca^{2+}-binding proteins
SNARE-associated proteins
Proteins involved in endocytosis
Proteins that form channels, transporters, or receptors
GTP-binding proteins
Miscellaneous important proteins
Synaptobrevin
Synaptic vesicle membrane
Synaptic vesicle
Cysteine string protein
Ca^{2+}/CaM dependent protein kinase II
Synaptotagmin
SV2
Synaptophysin
Synapsin
Snapin
Rab 3
Rabphilin
Dynamin
SNAP
Syndapin
Amphiphysin
AP180
Complexin
RIM
Synaptojanin
Clathrin
NSF
AP–2
DOC2
Tomosyn
nSec1
Hsc70
Auxilin
Syntaphilin
Ca^{2+} channel
Syntaxin
SNAP–25
Neurexin I
CLI
Cytoplasm
Plasma membrane of presynaptic terminal
Synaptic cleft

Figure 5.13 Presynaptic proteins implicated in neurotransmitter release. Structures adapted from Brunger (2001) and Brodsky et al. (2001).

complexin, nSec-1, snapin, syntaphilin, and tomosyn, bind to the SNAREs and presumably regulate the formation or disassembly of this complex.

Because the SNARE proteins do not bind Ca^{2+}, still other molecules must be responsible for Ca^{2+} regulation of neurotransmitter release. Several presynaptic proteins, including calmodulin, CAPS, and munc-13, are capable of binding Ca^{2+}. However, the leading candidate for Ca^{2+} regulation of neurotransmitter release is **synaptotagmin**, a protein found in the membrane of synaptic vesicles. Synaptotagmin binds Ca^{2+} at concentrations similar to those required to trigger vesicle fusion within the presynaptic terminal. It may act as a Ca^{2+} sensor, signaling the elevation of Ca^{2+} within the terminal and thus triggering vesicle fusion. In support of this idea, alterations of the properties of synaptotagmin in the presynaptic terminals of mice, fruit flies, squid, and other experimental animals impair Ca^{2+}-dependent neurotransmitter release. In fact, deletion of only one of the 19 synaptotagmin genes of mice is a lethal mutation, causing the mice to die soon after birth. How Ca^{2+} binding to synaptotagmin could lead to exocytosis is not yet clear. It is known that Ca^{2+} changes the chemical properties of synaptotagmin, allowing it to insert into membranes and to bind to other proteins, including the SNAREs. A plausible model is that the SNARE proteins bring the two membranes close together, and that Ca^{2+}-induced changes in synaptotagmin then produce the final fusion of these membranes (Figure 5.14B).

Still other proteins appear to be involved at subsequent steps of the synaptic vesicle cycle (Figure 5.14C). For example, the protein **clathrin** is involved in endocytotic budding of vesicles from the plasma membrane. Clathrin forms structures that resemble geodesic domes (Figure 5.14D); these structures form coated pits that initiate membrane budding. Assembly of individual clathrin triskelia (so named because of their 3-legged appearance) into coats is aided by several other accessory proteins, such as AP2, AP180 and amphiphysin. The coats increase the curvature of the budding membrane until it forms a coated vesicle-like structure. Another protein, called **dynamin**, is at least partly responsible for the final pinching-off of membrane to convert the coated pits into coated vesicles. The coats are then removed by an ATPase, **Hsc70**, with another protein called **auxilin** serving as a co-factor. Other proteins, such as **synaptojanin**, are also important for vesicle uncoating. Several lines of evidence indicate that the protein **synapsin**, which reversibly binds to synaptic vesicles, may cross-link newly formed vesicles to the cytoskeleton to keep the vesicles tethered within the reserve pool. Mobilization of these reserve pool vesicles is caused by phosphorylation of synapsin by proteins kinases (Chapter 7), which allows synapsin to dissociate from the vesicles, thus freeing the vesicles to make their way to the plasma membrane.

In summary, a complex cascade of proteins, acting in a defined temporal and spatial order, allows neurons to secrete transmitters. Although the detailed mechanisms responsible for transmitter secretion are not completely clear, rapid progress is being made toward this goal.

Neurotransmitter Receptors

The generation of postsynaptic electrical signals is also understood in considerable depth. Such studies began in 1907, when the British physiologist John N. Langley introduced the concept of **receptor molecules** to explain the specific and potent actions of certain chemicals on muscle and nerve cells. Much subsequent work has shown that receptor molecules do indeed account for the ability of neurotransmitters, hormones, and drugs to alter the

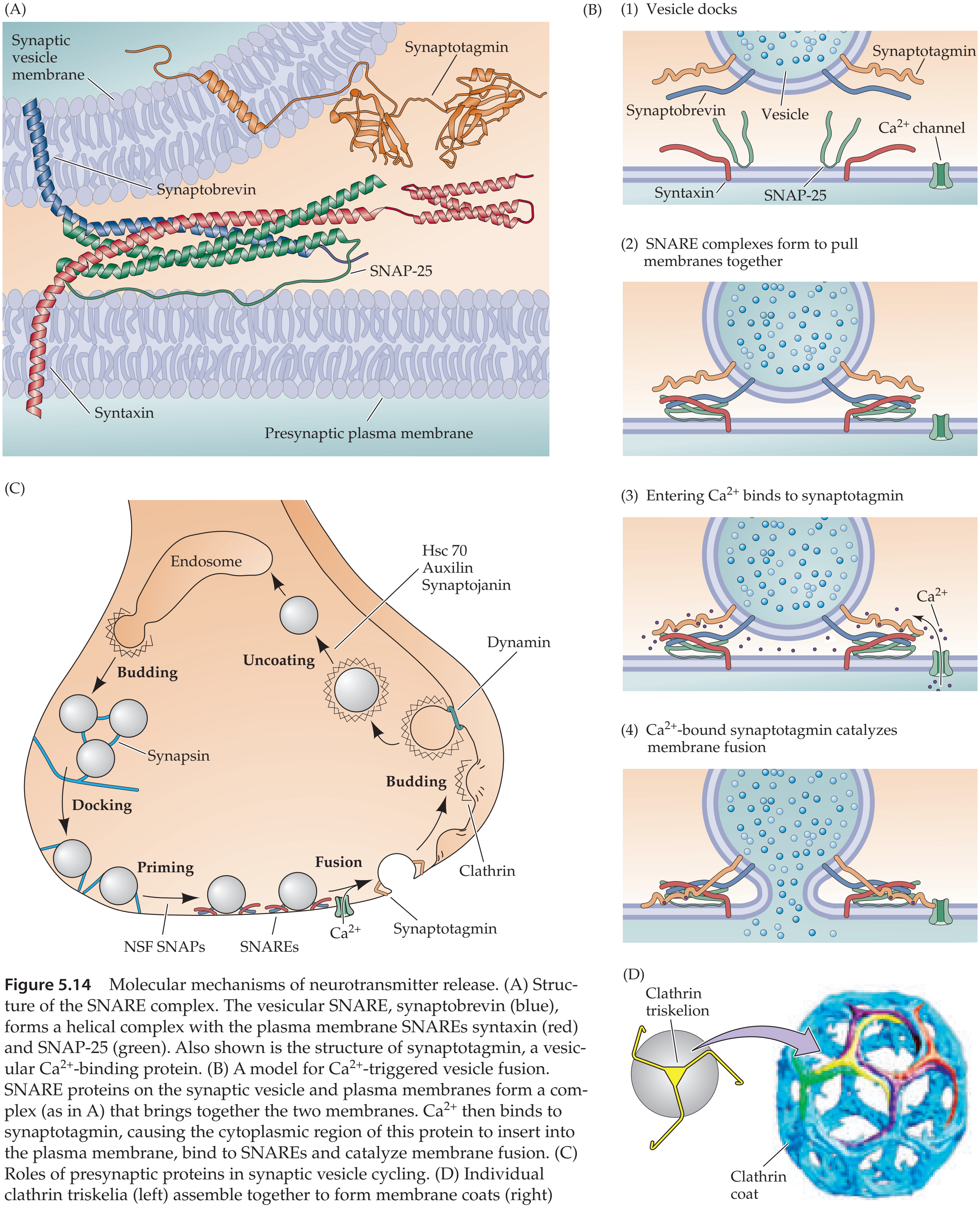

(A)
Synaptic vesicle membrane
Synaptotagmin
Synaptobrevin
SNAP-25
Syntaxin
Presynaptic plasma membrane
(B)
(1) Vesicle docks
Synaptotagmin
Synaptobrevin
Vesicle
Ca2+ channel
Syntaxin
SNAP-25
(2) SNARE complexes form to pull membranes together
(3) Entering Ca2+ binds to synaptotagmin
Ca2+
(4) Ca2+-bound synaptotagmin catalyzes membrane fusion
(C)
Endosome
Hsc 70
Auxilin
Synaptojanin
Uncoating
Budding
Dynamin
Synapsin
Budding
Docking
Priming
Fusion
Clathrin
NSF SNAPs
SNAREs
Ca2+
Synaptotagmin
(D)
Clathrin triskelion
Clathrin coat

Figure 5.14 Molecular mechanisms of neurotransmitter release. (A) Structure of the SNARE complex. The vesicular SNARE, synaptobrevin (blue), forms a helical complex with the plasma membrane SNAREs syntaxin (red) and SNAP-25 (green). Also shown is the structure of synaptotagmin, a vesicular Ca^{2+}-binding protein. (B) A model for Ca^{2+}-triggered vesicle fusion. SNARE proteins on the synaptic vesicle and plasma membranes form a complex (as in A) that brings together the two membranes. Ca^{2+} then binds to synaptotagmin, causing the cytoplasmic region of this protein to insert into the plasma membrane, bind to SNAREs and catalyze membrane fusion. (C) Roles of presynaptic proteins in synaptic vesicle cycling. (D) Individual clathrin triskelia (left) assemble together to form membrane coats (right) involved in membrane budding during endocytosis. (A after Sutton et al., 1998; C after Sudhof, 1995; D after Marsh and McMahon, 2001.)

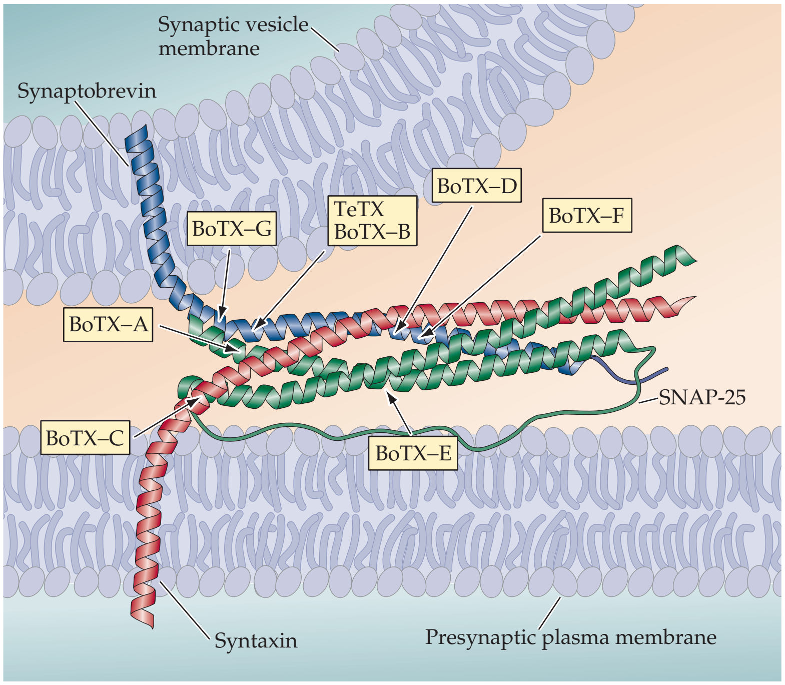
Box C

Toxins That Affect Transmitter Release

Several important insights about the molecular basis of neurotransmitter secretion have come from analyzing the actions of a series of biological toxins produced by a fascinating variety of organisms. One family of such agents is the clostridial toxins responsible for botulism and tetanus (see Box B). Clever and patient biochemical work has shown that these toxins are highly specific proteases that cleave presynaptic SNARE proteins (see figure). Tetanus toxin and botulinum toxin (types B, D, F, and G) specifically cleave the vesicle SNARE protein, synaptobrevin. Other botulinum toxins are proteases that cleave syntaxin (type C) and SNAP-25 (types A and E), SNARE proteins found on the presynaptic plasma membrane. Destruction of these presynaptic proteins is the basis for the actions of the toxins on neurotransmitter release. The evidence described in the text also implies that these three synaptic SNARE proteins are somehow important in the process of vesicle–plasma membrane fusion.

Another toxin that targets neurotransmitter release is α-latrotoxin, a protein found in the venom of the female black widow spider. Application of this molecule to neuromuscular synapses causes a massive discharge of synaptic vesicles, even when Ca^{2+} is absent from the extracellular medium. While it is not yet clear how this toxin triggers Ca^{2+}-independent exocytosis, α-latrotoxin binds to two different types of presynaptic proteins that may mediate its actions. One group of binding partners for α-latrotoxin is the neurexins, a group of integral membrane proteins found in presynaptic terminals (see Figure 5.13). Several lines of evidence implicate binding to neurexins in at least some of the actions of α-latrotoxin. Because the neurexins bind to synaptotagmin, a vesicular Ca^{2+}-binding protein that is known to be important in exocytosis, this interaction may allow α-latrotoxin to bypass the usual Ca^{2+} requirement for triggering vesicle fusion. Another type of presynaptic protein that can bind to α-latrotoxin is called CL1 (based on its previous names, *C*a^{2+}-*i*ndependent receptor for latrotoxin and *l*atrophilin-*1*). CL1 is a relative of the G-protein-coupled receptors that mediate the actions of neurotransmitters and other extracellular chemical signals (see Chapter 7). Thus, the binding of α-latrotoxin to CL1 is thought to activate an intracellular signal transduction cascade that may be involved in the Ca^{2+}-independent actions of α-latrotoxin. While more work is needed to establish the roles of neurexins and CL1 in the actions of α-latrotoxin definitively, effects on these two proteins probably account for the potent presynaptic actions of this toxin.

Still other toxins produced by snakes, snails, spiders, and other predatory animals are known to affect transmitter release, but their sites of action have yet to be identified. Based on the precedents described here, it is likely that these biological poisons will continue to provide valuable tools for elucidating the molecular basis of neurotransmitter release, just as they will continue to enable the predators to feast on their prey.



Cleavage of SNARE proteins by clostridial toxins. Indicated are the sites of proteolysis by tetanus toxin (TeTX) and various types of botulinum toxin (BoTX). (After Sutton et al., 1998.)

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functional properties of neurons. While it has been clear since Langley's day that receptors are important for synaptic transmission, their identity and detailed mechanism of action remained a mystery until quite recently. It is now known that neurotransmitter receptors are proteins embedded in the plasma membrane of postsynaptic cells. Domains of receptor molecules that extend into the synaptic cleft bind neurotransmitters that are released into this space by the presynaptic neuron. The binding of neurotransmitters, either directly or indirectly, causes ion channels in the postsynaptic membrane to open or close. Typically, the resulting ion fluxes change the membrane potential of the postsynaptic cell, thus mediating the transfer of information across the synapse.

Postsynaptic Membrane Permeability Changes during Synaptic Transmission

Just as studies of the neuromuscular synapse paved the way for understanding neurotransmitter release mechanisms, this peripheral synapse has been equally valuable for understanding the mechanisms that allow neurotransmitter receptors to generate postsynaptic signals. The binding of ACh to postsynaptic receptors opens ion channels in the muscle fiber membrane. This effect can be demonstrated directly by using the patch clamp method (see Box A in Chapter 4) to measure the minute postsynaptic currents that flow when two molecules of individual ACh bind to receptors, as Erwin Neher and Bert Sakmann first did in 1976. Exposure of the extracellular surface of a patch of postsynaptic membrane to ACh causes single-channel currents to flow for a few milliseconds (Figure 5.15A). This shows that ACh binding to its receptors opens ligand-gated ion channels, much in the way that changes in membrane potential open voltage-gated ion channels (Chapter 4).

The electrical actions of ACh are greatly multiplied when an action potential in a presynaptic motor neuron causes the release of millions of molecules of ACh into the synaptic cleft. In this more physiological case, the transmitter molecules bind to many thousands of ACh receptors packed in a dense array on the postsynaptic membrane, transiently opening a very large number of postsynaptic ion channels. Although individual ACh receptors only open briefly, (Figure 5.15B1), the opening of a large number of channels is synchronized by the brief duration during which ACh is secreted from presynaptic terminals (Figure 5.15B2,3). The macroscopic current resulting from the summed opening of many ion channels is called the **end plate current**, or **EPC**. Because the current flowing during the EPC is normally inward, it causes the postsynaptic membrane potential to depolarize. This depolarizing change in potential is the EPP (Figure 5.15C), which typically triggers a postsynaptic action potential by opening voltage-gated Na^+ and K^+ channels (see Figure 5.6B).

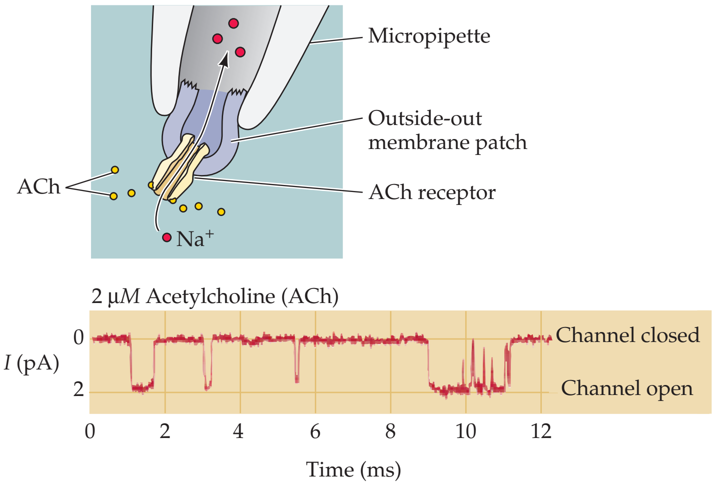
The identity of the ions that flow during the EPC can be determined via the same approaches used to identify the roles of Na^+ and K^+ fluxes in the currents underlying action potentials (Chapter 3). Key to such an analysis is identifying the membrane potential at which no current flows during transmitter action. When the potential of the postsynaptic muscle cell is controlled by the voltage clamp method (Figure 5.16A), the magnitude of the membrane potential clearly affects the amplitude and polarity of EPCs (Figure 5.16B). Thus, when the postsynaptic membrane potential is made more negative than the resting potential, the amplitude of the EPC becomes larger, whereas this current is reduced when the membrane potential is made more positive. At approximately 0 mV, no EPC is detected, and at even more positive potentials, the current reverses its polarity, becoming outward rather than inward (Figure 5.16C). The potential where the EPC reverses, about 0 mV in the case of the neuromuscular junction, is called the **reversal potential**.

As was the case for currents flowing through voltage-gated ion channels (see Chapter 3), the magnitude of the EPC at any membrane potential is given by the product of the ionic conductance activated by ACh (g_{ACh}) and the electrochemical driving force on the ions flowing through ligand-gated channels. Thus, the value of the EPC is given by the relationship

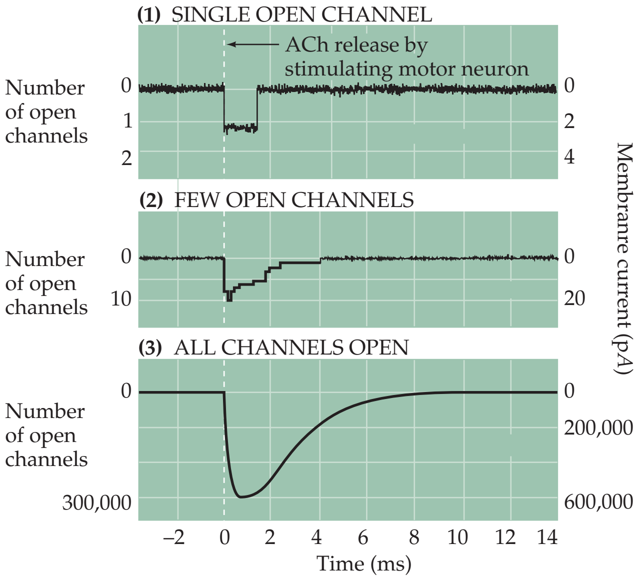
$$\text{EPC} = g_{\text{ACh}}(V_{\text{m}} - E_{\text{rev}})$$

where E_{rev} is the reversal potential for the EPC. This relationship predicts that the EPC will be an inward current at potentials more negative than E_{rev} because the electrochemical driving force, $V_{\text{m}} - E_{\text{rev}}$, is a negative number. Further, the EPC will become smaller at potentials approaching E_{rev} because the driving force is reduced. At potentials more positive than E_{rev}, the EPC is outward because the driving force is reversed in direction (that is, positive). Because the channels opened by ACh are largely insensitive to membrane voltage, g_{ACh} will depend only on the number of channels opened by ACh, which depends in turn on the concentration of ACh in the synaptic cleft.

(A) Patch clamp measurement of single ACh receptor current



(B) Currents produced by:



(C) Postsynaptic potential change (EPP) produced by EPC

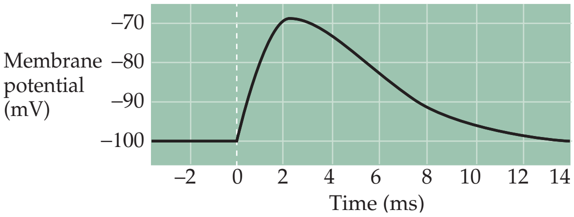


Figure 5.15 Activation of ACh receptors at neuromuscular synapses. (A) Outside-out patch clamp measurement of single ACh receptor currents from a patch of membrane removed from the postsynaptic muscle cell. When ACh is applied to the extracellular surface of the membrane clamped at negative voltages, the repeated brief opening of a single channel can be seen as downward deflections corresponding to inward current (i.e., positive ions flowing into the cell). (B) Synchronized opening of many ACh-activated channels at a synapse being voltage-clamped at negative voltages. (1) If a single channel is examined during the release of ACh from the presynaptic terminal, the channel opens transiently. (2) If a number of channels are examined together, ACh release opens the channels almost synchronously. (3) The opening of a very large number of postsynaptic channels produces a macroscopic EPC. (C) In a normal muscle cell (i.e., not being voltage-clamped), the inward EPC depolarizes the postsynaptic muscle cell, giving rise to an EPP. Typically, this depolarization generates an action potential (not shown).

Thus, the magnitude and polarity of the postsynaptic membrane potential determines the direction and amplitude of the EPC solely by altering the driving force on ions flowing through the receptor channels opened by ACh.

When V_m is at the reversal potential, $V_m - E_{rev}$ is equal to 0 and there is no net driving force on the ions that can permeate the receptor-activated channel. As a result, the identity of the ions that flow during the EPC can be deduced by observing how the reversal potential of the EPC compares to the equilibrium potential for various ion species (Figure 5.17). For example, if ACh were to open an ion channel permeable only to K^+, then the reversal

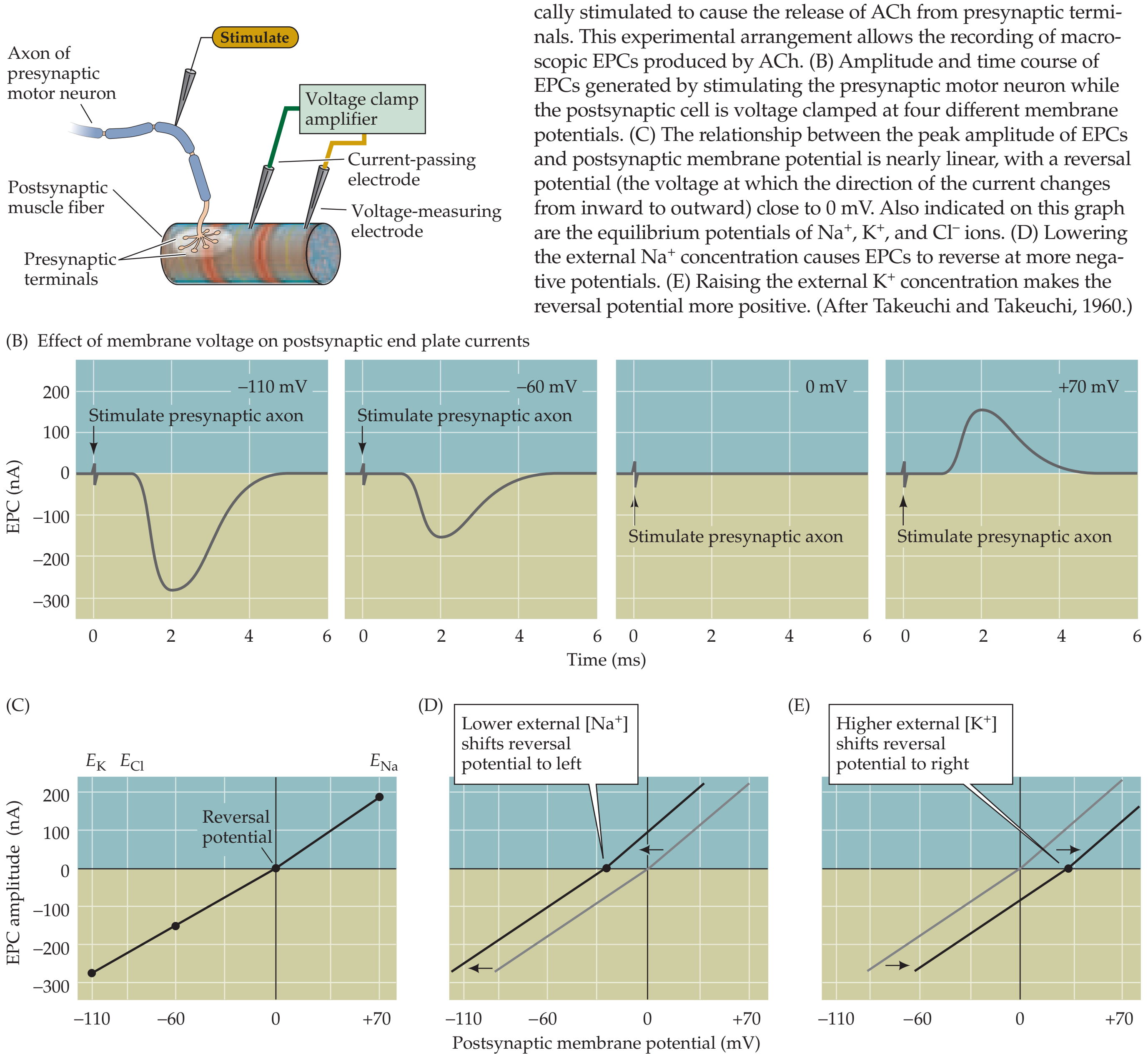


Figure 5.16 The influence of the postsynaptic membrane potential on end plate currents. (A) A postsynaptic muscle fiber is voltage clamped using two electrodes, while the presynaptic neuron is electrically stimulated to cause the release of ACh from presynaptic terminals. This experimental arrangement allows the recording of macroscopic EPCs produced by ACh. (B) Amplitude and time course of EPCs generated by stimulating the presynaptic motor neuron while the postsynaptic cell is voltage clamped at four different membrane potentials. (C) The relationship between the peak amplitude of EPCs and postsynaptic membrane potential is nearly linear, with a reversal potential (the voltage at which the direction of the current changes from inward to outward) close to 0 mV. Also indicated on this graph are the equilibrium potentials of Na^+, K^+, and Cl^- ions. (D) Lowering the external Na^+ concentration causes EPCs to reverse at more negative potentials. (E) Raising the external K^+ concentration makes the reversal potential more positive. (After Takeuchi and Takeuchi, 1960.)

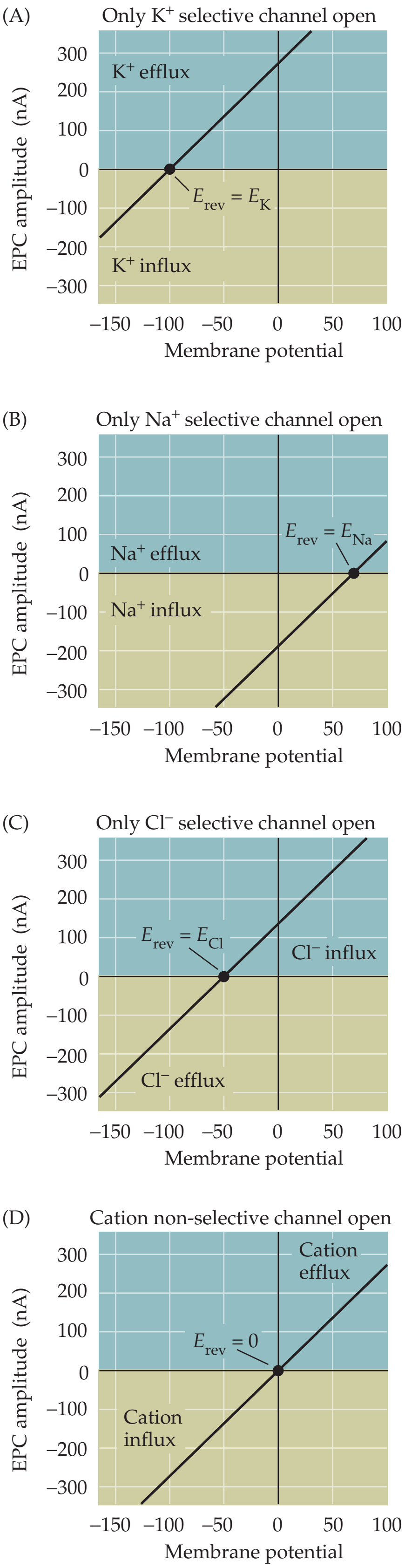


Figure 5.17 The effect of ion channel selectivity on the reversal potential. Voltage clamping a postsynaptic cell while activating presynaptic neurotransmitter release reveals the identity of the ions permeating the postsynaptic receptors being activated. (A) The activation of postsynaptic channels permeable only to K^+ results in currents reversing at E_K, near –100 mV. (B) The activation of postsynaptic Na^+ channels results in currents reversing at E_{Na}, near +70 mV. (C) Cl^--selective currents reverse at E_{Cl}, near –50 mV. (D) Ligand-gated channels that are about equally permeable to both K^+ and Na^+ show a reversal potential near 0 mV.

potential of the EPC would be at the equilibrium potential for K^+, which for a muscle cell is close to –100 mV (Figure 5.17A). If the ACh-activated channels were permeable only to Na^+, then the reversal potential of the current would be approximately +70 mV, the Na^+ equilibrium potential of muscle cells (Figure 5.17B); if these channels were permeable only to Cl^-, then the reversal potential would be approximately –50 mV (Figure 5.17C). By this reasoning, ACh-activated channels cannot be permeable to only one of these ions, because the reversal potential of the EPC is not near the equilibrium potential for any of them (see Figure 5.16C). However, if these channels were permeable to both Na^+ and K^+, then the reversal potential of the EPC would be between +70 mV and –100 mV (Figure 5.17D).

The fact that EPCs reverse at approximately 0 mV is therefore consistent with the idea that ACh-activated ion channels are almost equally permeable to both Na^+ and K^+. This was tested in 1960, by the husband and wife team of Akira and Noriko Takeuchi, by altering the extracellular concentration of these two ions. As predicted, the magnitude and reversal potential of the EPC was changed by altering the concentration gradient of each ion. Lowering the external Na^+ concentration, which makes E_{Na} more negative, produces a negative shift in E_{rev} (Figure 5.16D), whereas elevating external K^+ concentration, which makes E_K more positive, causes E_{rev} to shift to a more positive potential (Figure 5.16E). Such experiments confirm that the ACh-activated ion channels are in fact permeable to both Na^+ and K^+.

Even though the channels opened by the binding of ACh to its receptors are permeable to both Na^+ and K^+, at the resting membrane potential the EPC is generated primarily by Na^+ influx (Figure 5.18). If the membrane potential is kept at E_K, the EPC arises entirely from an influx of Na^+ because at this potential there is no driving force on K^+ (Figure 5.18A). At the usual muscle fiber resting membrane potential of –90 mV, there is a small driving force on K^+, but a much greater one on Na^+. Thus, during the EPC, much more Na^+ flows into the muscle cell than K^+ flows out (Figure 5.18B); it is the net influx of positively charged Na^+ that constitutes the inward current measured as the EPC. At the reversal potential of about 0 mV, Na^+ influx and K^+ efflux are exactly balanced, so no current flows during the opening of channels by ACh binding (Figure 5.18C). At potentials more positive than E_{rev} the balance reverses; for example, at E_{Na} there is no influx of Na^+ and a large efflux of K^+ because of the large driving force on Na^+ (Figure 5.18D). Even more positive potentials cause efflux of both Na^+ and K^+ and produce an even larger outward EPC.

Were it possible to measure the EPP at the same time as the EPC (of course, the voltage clamp technique prevents this by keeping membrane potential constant), the EPP would be seen to vary in parallel with the amplitude and polarity of the EPC (Figures 5.18E,F). At the usual postsynaptic resting membrane potential of –90 mV, the large inward EPC causes the postsynaptic membrane potential to become more depolarized (see Figure

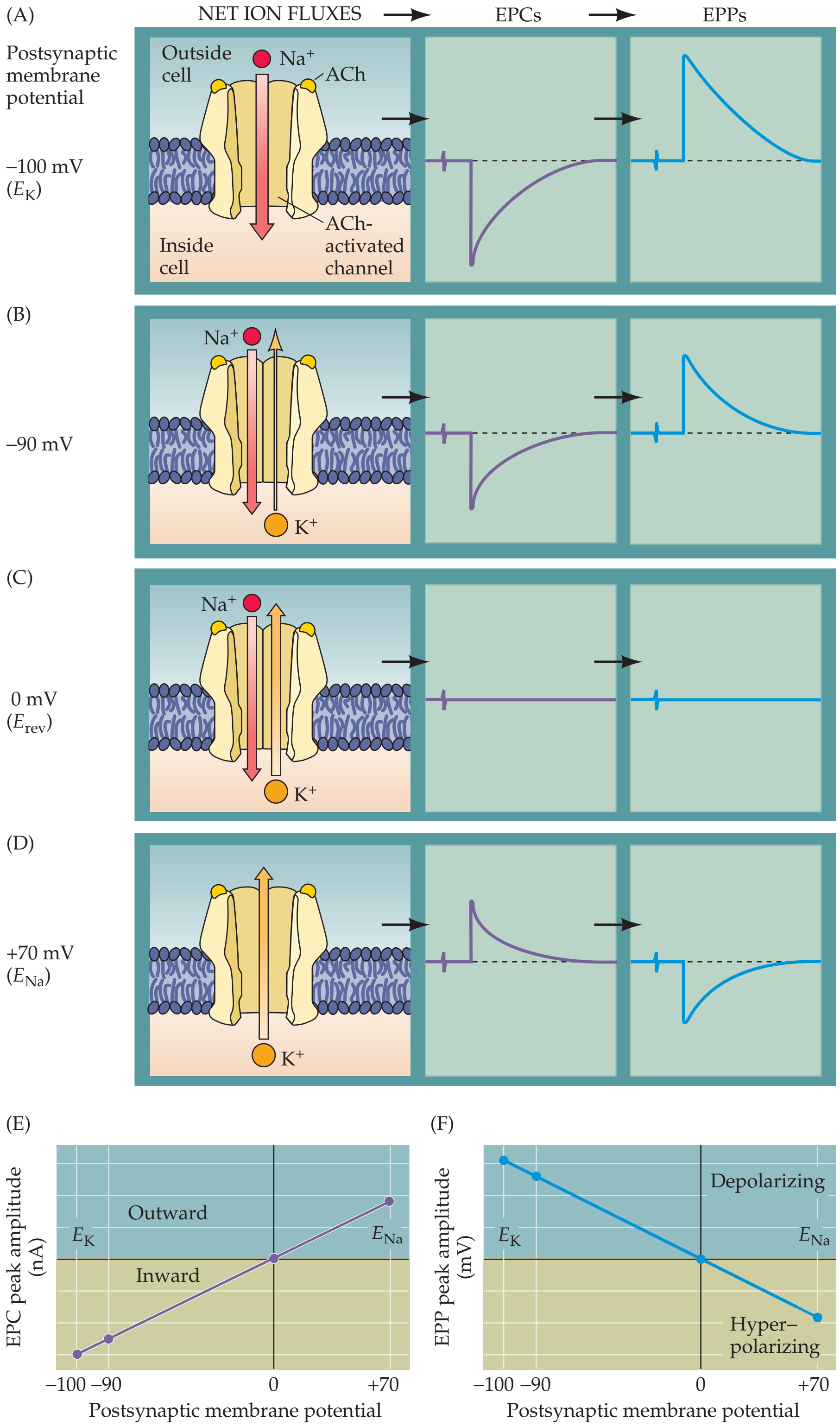

(A)
NET ION FLUXES
EPCs
EPPs
Postsynaptic membrane potential
Outside cell
Na+
ACh
−100 mV (E_K)
Inside cell
ACh-activated channel
(B)
Na+
−90 mV
K+
(C)
Na+
0 mV (E_{rev})
K+
(D)
+70 mV (E_{Na})
K+
(E)
EPC peak amplitude (nA)
Outward
Inward
E_K
E_{Na}
−100 −90
0
+70
Postsynaptic membrane potential
(F)
EPP peak amplitude (mV)
Depolarizing
Hyper–polarizing
E_K
E_{Na}
−100 −90
0
+70
Postsynaptic membrane potential

Figure 5.18 Na^+ and K^+ movements during EPCs and EPPs. (A–D) Each of the postsynaptic potentials (V_{post}) indicated at the left results in different relative fluxes of net Na^+ and K^+ (ion fluxes). These ion fluxes determine the amplitude and polarity of the EPCs, which in turn determine the EPPs. Note that at about 0 mV the Na^+ flux is exactly balanced by an opposite K^+ flux, resulting in no net current flow, and hence no change in the membrane potential. (E) EPCs are inward currents at potentials more negative than E_{rev} and outward currents at potentials more positive than E_{rev}. (F) EPPs depolarize the postsynaptic cell at potentials more negative than E_{rev}. At potentials more positive than E_{rev}, EPPs hyperpolarize the cell.

5.18F). However, at 0 mV, the EPP reverses its polarity, and at more positive potentials, the EPP is hyperpolarizing. Thus, the polarity and magnitude of the EPC depend on the electrochemical driving force, which in turn determines the polarity and magnitude of the EPP. EPPs will depolarize when the membrane potential is more negative than E_{rev}, and hyperpolarize when the membrane potential is more positive than E_{rev}. The general rule, then, is that *the action of a transmitter drives the postsynaptic membrane potential toward* E_{rev} *for the particular ion channels being activated*.

Although this discussion has focused on the neuromuscular junction, similar mechanisms generate postsynaptic responses at all chemical synapses. The general principle is that transmitter binding to postsynaptic receptors produces a postsynaptic conductance change as ion channels are opened (or sometimes closed). The postsynaptic conductance is increased if—as at the neuromuscular junction—channels are opened, and decreased if channels are closed. This conductance change typically generates an electrical current, the **postsynaptic current** (**PSC**), which in turn changes the postsynaptic membrane potential to produce a **postsynaptic potential** (**PSP**). As in the specific case of the EPP at the neuromuscular junction, PSPs are depolarizing if their reversal potential is more positive than the postsynaptic membrane potential and hyperpolarizing if their reversal potential is more negative.

The conductance changes and the PSPs that typically accompany them are the ultimate outcome of most chemical synaptic transmission, concluding a sequence of electrical and chemical events that begins with the invasion of an action potential into the terminals of a presynaptic neuron. In many ways, the events that produce PSPs at synapses are similar to those that generate action potentials in axons; in both cases, conductance changes produced by ion channels lead to ionic current flow that changes the membrane potential (see Figure 5.18).

Excitatory and Inhibitory Postsynaptic Potentials

PSPs ultimately alter the probability that an action potential will be produced in the postsynaptic cell. At the neuromuscular junction, synaptic action increases the probability that an action potential will occur in the postsynaptic muscle cell; indeed, the large amplitude of the EPP ensures that an action potential always is triggered. At many other synapses, PSPs similarly increase the probability of firing a postsynaptic action potential. However, still other synapses actually *decrease* the probability that the postsynaptic cell will generate an action potential. PSPs are called **excitatory** (or **EPSPs**) if they increase the likelihood of a postsynaptic action potential occurring, and **inhibitory** (or **IPSPs**) if they decrease this likelihood. Given that most neurons receive inputs from both excitatory and inhibitory synapses, it is important to understand more precisely the mechanisms that determine whether a particular synapse excites or inhibits its postsynaptic partner.

The principles of excitation just described for the neuromuscular junction are pertinent to all excitatory synapses. The principles of postsynaptic inhibition are much the same as for excitation, and are also quite general. In both cases, neurotransmitters binding to receptors open or close ion channels in the postsynaptic cell. Whether a postsynaptic response is an EPSP or an IPSP depends on the type of channel that is coupled to the receptor, and on the concentration of permeant ions inside and outside the cell. In fact, the only distinction between postsynaptic excitation and inhibition is the reversal potential of the PSP in relation to the threshold voltage for generating action potentials in the postsynaptic cell.

Consider, for example, a neuronal synapse that uses glutamate as the transmitter. Many such synapses have receptors that, like the ACh receptors at neuromuscular synapses, open ion channels that are nonselectively permeable to cations (see Chapter 6). When these glutamate receptors are activated, both Na^+ and K^+ flow across the postsynaptic membrane, yielding an E_{rev} of approximately 0 mV for the resulting postsynaptic current. If the rest-

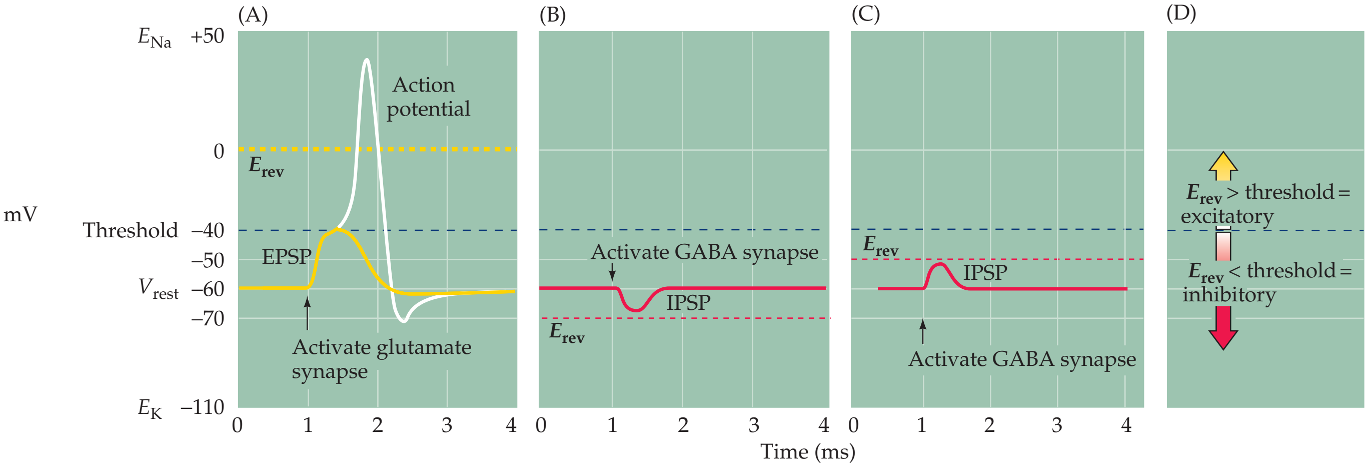


Figure 5.19 Reversal potentials and threshold potentials determine postsynaptic excitation and inhibition. (A) If the reversal potential for a PSP (0 mV) is more positive than the action potential threshold (–40 mV), the effect of a transmitter is excitatory, and it generates EPSPs. (B) If the reversal potential for a PSP is more negative than the action potential threshold, the transmitter is inhibitory and generate IPSPs. (C) IPSPs can nonetheless depolarize the postsynaptic cell if their reversal potential is between the resting potential and the action potential threshold. (D) The general rule of postsynaptic action is: If the reversal potential is more positive than threshold, excitation results; inhibition occurs if the reversal potential is more negative than threshold.

ing potential of the postsynaptic neuron is –60 mV, the resulting EPSP will depolarize by bringing the postsynaptic membrane potential toward 0 mV. For the hypothetical neuron shown in Figure 5.19A, the action potential threshold voltage is –40 mV. Thus, a glutamate-induced EPSP will increase the probability that this neuron produces an action potential, defining the synapse as excitatory.

As an example of inhibitory postsynaptic action, consider a neuronal synapse that uses GABA as its transmitter. At such synapses, the GABA receptors typically open channels that are selectively permeable to Cl^- and the action of GABA causes Cl^- to flow across the postsynaptic membrane. Consider a case where E_{Cl} is –70 mV, as is typical for many neurons, so that the postsynaptic resting potential of –60 mV is less negative than E_{Cl}. The resulting positive electrochemical driving force ($V_m - E_{rev}$) will cause negatively charged Cl^- to flow into the cell and produce a hyperpolarizing IPSP (Figure 5.19B). This hyperpolarizing IPSP will take the postsynaptic membrane away from the action potential threshold of –40 mV, clearly inhibiting the postsynaptic cell.

Surprisingly, inhibitory synapses need not produce hyperpolarizing IPSPs. For instance, if E_{Cl} were –50 mV instead of –70 mV, then the negative electrochemical driving force would cause Cl^- to flow out of the cell and produce a depolarizing IPSP (Figure 5.19C). However, the synapse would still be inhibitory: Given that the reversal potential of the IPSP still is more negative than the action potential threshold (–40 mV), the depolarizing IPSP would inhibit because the postsynaptic membrane potential would be kept more negative than the threshold for action potential initiation. Another way to think about this peculiar situation is that if another excitatory input onto this neuron brought the cell's membrane potential to –41 mV, just below threshold for firing an action potential, the IPSP would then hyperpolarize the membrane potential toward –50 mV, bringing the potential away from the action potential threshold. Thus, while EPSPs depolarize the postsynaptic cell, IPSPs can hyperpolarize or depolarize; indeed, an inhibitory conductance change may produce no potential change at all and still exert an inhibitory effect by making it more difficult for an EPSP to evoke an action potential in the postsynaptic cell.

Although the particulars of postsynaptic action can be complex, a simple rule distinguishes postsynaptic excitation from inhibition: An EPSP has a reversal potential more positive than the action potential threshold, whereas an IPSP has a reversal potential more negative than threshold (Figure 5.19D). Intuitively, this rule can be understood by realizing that an EPSP will tend to depolarize the membrane potential so that it exceeds threshold, whereas an IPSP will always act to keep the membrane potential more negative than the threshold potential.

Summation of Synaptic Potentials

The PSPs produced at most synapses in the brain are much smaller than those at the neuromuscular junction; indeed, EPSPs produced by individual excitatory synapses may be only a fraction of a millivolt and are usually well below the threshold for generating postsynaptic action potentials. How, then, can such synapses transmit information if their PSPs are subthreshold? The answer is that neurons in the central nervous system are typically innervated by thousands of synapses, and the PSPs produced by each active synapse can *sum together*—in space and in time—to determine the behavior of the postsynaptic neuron.

Consider the highly simplified case of a neuron that is innervated by two excitatory synapses, each generating a subthreshold EPSP, and an inhibitory synapse that produces an IPSP (Figure 5.20A). While activation of either one of the excitatory synapses alone (E1 or E2 in Figure 5.20B) produces a sub-

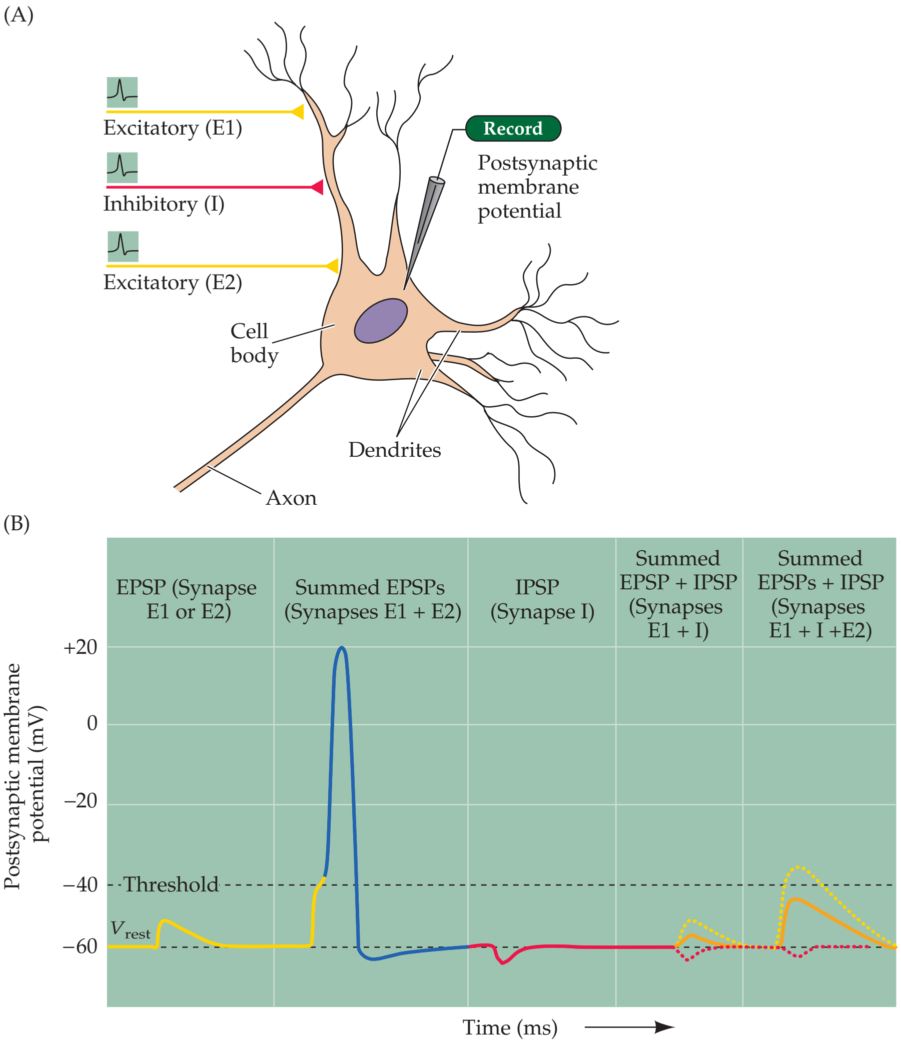

(A)
Excitatory (E1)
Inhibitory (I)
Excitatory (E2)
Record
Postsynaptic membrane potential
Cell body
Dendrites
Axon
(B)
EPSP (Synapse E1 or E2)
Summed EPSPs (Synapses E1 + E2)
IPSP (Synapse I)
Summed EPSP + IPSP (Synapses E1 + I)
Summed EPSPs + IPSP (Synapses E1 + I +E2)
Postsynaptic membrane potential (mV)
+20
0
−20
−40
−60
Threshold
V_{rest}
Time (ms)

Figure 5.20 Summation of postsynaptic potentials. (A) A microelectrode records the postsynaptic potentials produced by the activity of two excitatory synapses (E1 and E2) and an inhibitory synapse (I). (B) Electrical responses to synaptic activation. Stimulating either excitatory synapse (E1 or E2) produces a subthreshold EPSP, whereas stimulating both synapses at the same time (E1 + E2) produces a suprathreshold EPSP that evokes a postsynaptic action potential (shown in blue). Activation of the inhibitory synapse alone (I) results in a hyperpolarizing IPSP. Summing this IPSP (dashed red line) with the EPSP (dashed yellow line) produced by one excitatory synapse (E1 + I) reduces the amplitude of the EPSP (orange line), while summing it with the suprathreshold EPSP produced by activating synapses E1 and E2 keeps the postsynaptic neuron below threshold, so that no action potential is evoked.

threshold EPSP, activation of both excitatory synapses at about the same time causes the two EPSPs to sum together. If the sum of the two EPSPs (E1 + E2) depolarizes the postsynaptic neuron sufficiently to reach the threshold potential, a postsynaptic action potential results. **Summation** thus allows subthreshold EPSPs to influence action potential production. Likewise, an IPSP generated by an inhibitory synapse (I) can sum (algebraically speaking) with a subthreshold EPSP to reduce its amplitude (E1 + I) or can sum with suprathreshold EPSPs to prevent the postsynaptic neuron from reaching threshold (E1 + I + E2).

In short, the summation of EPSPs and IPSPs by a postsynaptic neuron permits a neuron to integrate the electrical information provided by all the inhibitory and excitatory synapses acting on it at any moment. Whether the sum of active synaptic inputs results in the production of an action potential depends on the balance between excitation and inhibition. If the sum of all EPSPs and IPSPs results in a depolarization of sufficient amplitude to raise the membrane potential above threshold, then the postsynaptic cell will produce an action potential. Conversely, if inhibition prevails, then the postsynaptic cell will remain silent. Normally, the balance between EPSPs and IPSPs changes continually over time, depending on the number of excitatory and inhibitory synapses active at a given moment and the magnitude of the current at each active synapse. Summation is therefore a neurotransmitter-induced tug-of-war between all excitatory and inhibitory postsynaptic currents; the outcome of the contest determines whether or not a postsynaptic neuron fires an action potential and, thereby, becomes an active element in the neural circuits to which it belongs (Figure 5.21).

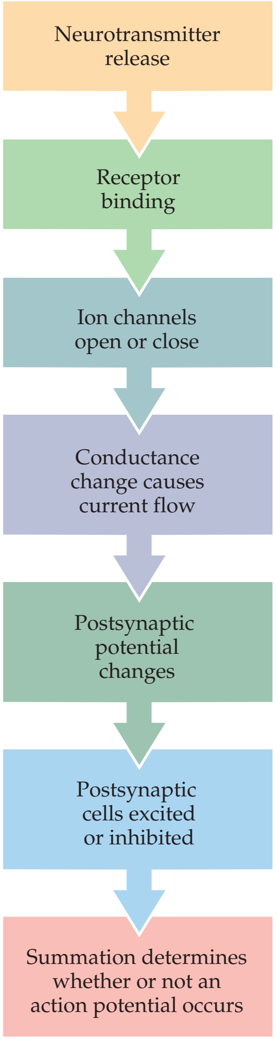

Neurotransmitter release
Receptor binding
Ion channels open or close
Conductance change causes current flow
Postsynaptic potential changes
Postsynaptic cells excited or inhibited
Summation determines whether or not an action potential occurs

Figure 5.21 Events from neurotransmitter release to postsynaptic excitation or inhibition. Neurotransmitter release at all presynaptic terminals on a cell results in receptor binding, which causes the opening or closing of specific ion channels. The resulting conductance change causes current to flow, which may change the membrane potential. The postsynaptic cell sums (or integrates) all of the EPSPs and IPSPs, resulting in moment-to-moment control of action potential generation.

Two Families of Postsynaptic Receptors

The opening or closing of postsynaptic ion channels is accomplished in different ways by two broad families of receptor proteins. The receptors in one family—called **ionotropic receptors**—are linked directly to ion channels (the Greek *tropos* means to move in response to a stimulus). These receptors contain two functional domains: an extracellular site that binds neurotransmitters, and a membrane-spanning domain that forms an ion channel (Figure 5.22A). Thus ionotropic receptors combine transmitter-binding and channel functions into a single molecular entity (they are also called **ligand-gated ion channels** to reflect this concatenation). Such receptors are multimers made up of at least four or five individual protein subunits, each of which contributes to the pore of the ion channel.

The second family of neurotransmitter receptors are the **metabotropic receptors,** so called because the eventual movement of ions through a channel depends on one or more metabolic steps. These receptors do not have ion channels as part of their structure; instead, they affect channels by the activation of intermediate molecules called **G-proteins** (Figure 5.22B). For this reason, metabotropic receptors are also called **G-protein-coupled receptors**. Metabotropic receptors are monomeric proteins with an extracellular domain that contains a neurotransmitter binding site and an intracellular domain that binds to G-proteins. Neurotransmitter binding to metabotropic receptors activates G-proteins, which then dissociate from the receptor and interact directly with ion channels or bind to other effector proteins, such as enzymes, that make intracellular messengers that open or close ion channels. Thus, G-proteins can be thought of as transducers that couple neurotransmitter binding to the regulation of postsynaptic ion channels. The postsynaptic signaling events initiated by metabotropic receptors are taken up in detail in Chapter 7.

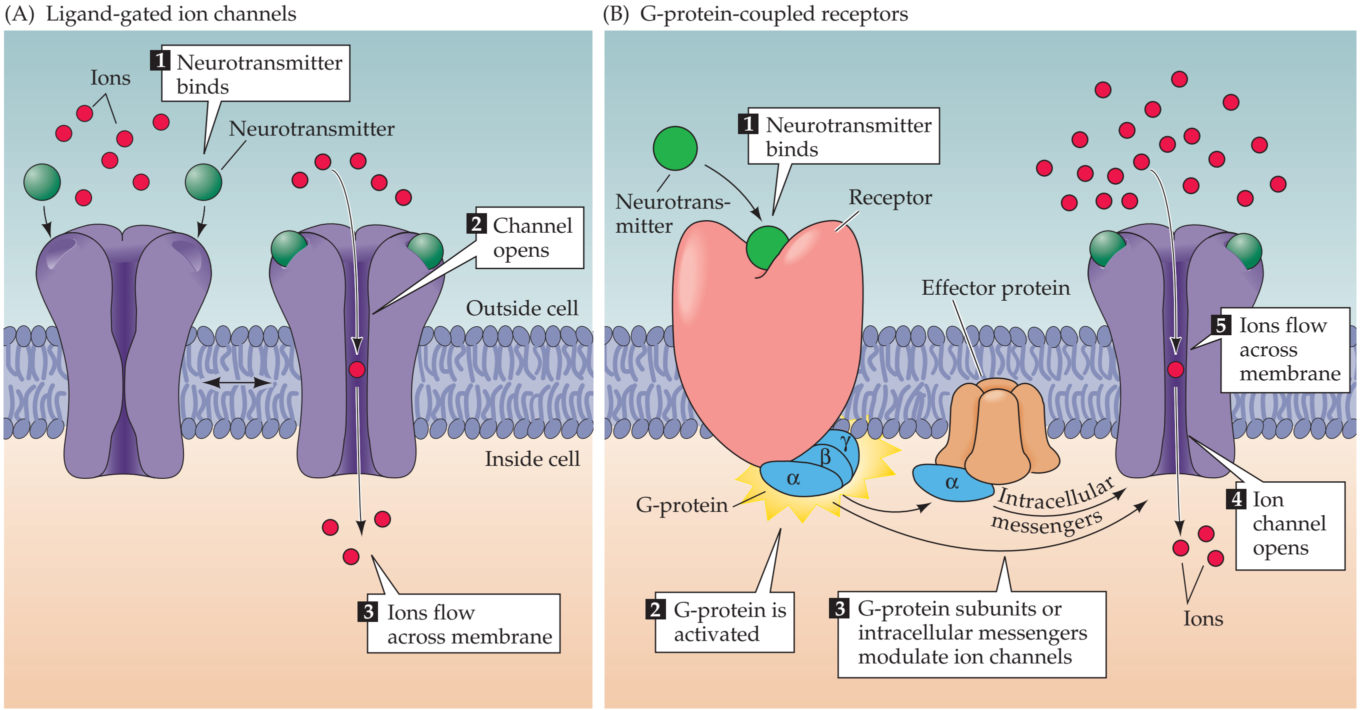

(A) Ligand-gated ion channels
Ions
1 Neurotransmitter binds
Neurotransmitter
2 Channel opens
Outside cell
Inside cell
3 Ions flow across membrane
(B) G-protein-coupled receptors
1 Neurotransmitter binds
Neurotrans-mitter
Receptor
Effector protein
5 Ions flow across membrane
β
γ
α
α
G-protein
Intracellular messengers
4 Ion channel opens
2 G-protein is activated
3 G-protein subunits or intracellular messengers modulate ion channels
Ions

Figure 5.22 A neurotransmitter can affect the activity of a postsynaptic cell via two different types of receptor proteins: ionotropic or ligand-gated ion channels, and metabotropic or G-protein-coupled receptors. (A) Ligand-gated ion channels combine receptor and channel functions in a single protein complex. (B) Metabotropic receptors usually activate G-proteins, which modulate ion channels directly or indirectly through intracellular effector enzymes and second messengers.

These two families of postsynaptic receptors give rise to PSPs with very different time courses, producing postsynaptic actions that range from less than a millisecond to minutes, hours, or even days. Ionotropic receptors generally mediate rapid postsynaptic effects. Examples are the EPP produced at neuromuscular synapses by ACh (see Figure 5.15), EPSPs produced at certain glutamatergic synapses (Figure 5.19A), and IPSPs produced at certain GABAergic synapses (Figure 5.19B). In all three cases, the PSPs arise within a millisecond or two of an action potential invading the presynaptic terminal and last for only a few tens of milliseconds or less. In contrast, the activation of metabotropic receptors typically produces much slower responses, ranging from hundreds of milliseconds to minutes or even longer. The comparative slowness of metabotropic receptor actions reflects the fact that multiple proteins need to bind to each other sequentially in order to produce the final physiological response. Importantly, a given transmitter may activate both ionotropic and metabotropic receptors to produce both fast and slow PSPs at the same synapse.

Perhaps the most important principle to keep in mind is that the response elicited at a given synapse depends upon the neurotransmitter released and the postsynaptic complement of receptors and associated channels. The molecular mechanisms that allow neurotransmitters and their receptors to generate synaptic responses are considered in the next chapter.

Summary

Synapses communicate the information carried by action potentials from one neuron to the next in neural circuits. The cellular mechanisms that underlie synaptic transmission are closely related to the mechanisms that generate other types of neuronal electrical signals, namely ion flow through membrane channels. In the case of electrical synapses, these channels are gap junctions; direct but passive flow of current through the gap junctions is the basis for transmission. In the case of chemical synapses, channels with smaller and more selective pores are activated by the binding of neurotransmitters to postsynaptic receptors after release from the presynaptic terminal. The large number of neurotransmitters in the nervous system can be divided into two broad classes: small-molecule transmitters and neuropeptides. Neurotransmitters are synthesized from defined precursors by regulated enzymatic pathways, packaged into one of several types of synaptic vesicle, and released into the synaptic cleft in a Ca^{2+}-dependent manner. Many synapses release more than one type of neurotransmitter, and multiple transmitters can even be packaged within the same synaptic vesicle. Transmitter agents are released presynaptically in units or quanta, reflecting their storage within synaptic vesicles. Vesicles discharge their contents into the synaptic cleft when the presynaptic depolarization generated by the invasion of an action potential opens voltage-gated calcium channels, allowing Ca^{2+} to enter the presynaptic terminal. How calcium triggers neurotransmitter release is not yet established, but synaptotagmin, SNAREs, and a number of other proteins found within the presynaptic terminal are clearly involved. Postsynaptic receptors are a diverse group of proteins that transduce binding of neurotransmitters into electrical signals by opening or closing postsynaptic ion channels. The postsynaptic currents produced by the synchronous opening or closing of ion channels changes the conductance of the postsynaptic cell, thus increasing or decreasing its excitability. Conductance changes that increase the probability of firing an action potential are excitatory, whereas those that decrease the probability of generating an action potential are inhibitory. Because postsynaptic neurons are usually innervated by many different inputs, the integrated effect of the conductance changes underlying all EPSPs and IPSPs produced in a postsynaptic cell at any moment determines whether or not the cell fires an action potential. Two broadly different families of neurotransmitter receptors have evolved to carry out the postsynaptic signaling actions of neurotransmitters. The postsynaptic effects of neurotransmitters are terminated by the degradation of the transmitter in the synaptic cleft, by transport of the transmitter back into cells, or by diffusion out of the synaptic cleft.

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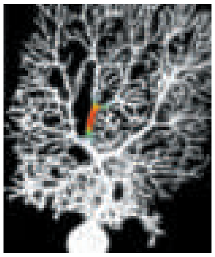
Chapter 6



Neurotransmitters and Their Receptors

Overview

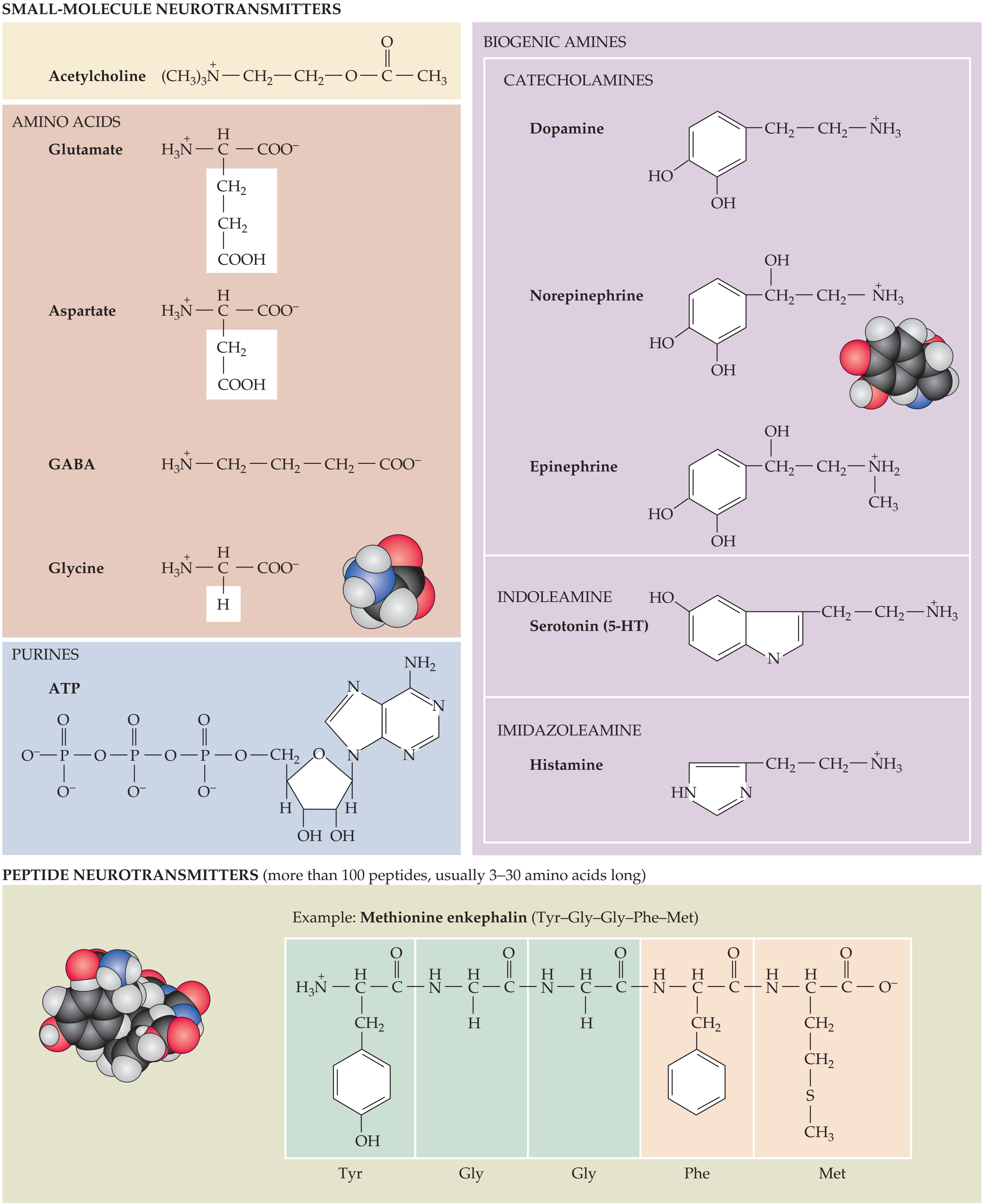
For the most part, neurons in the human brain communicate with one another by releasing chemical messengers called neurotransmitters. A large number of neurotransmitters are now known and more remain to be discovered. Neurotransmitters evoke postsynaptic electrical responses by binding to members of a diverse group of proteins called neurotransmitter receptors. There are two major classes of receptors: those in which the receptor molecule is also an ion channel, and those in which the receptor and ion channel are separate molecules. The former are called ionotropic receptors or ligand-gated ion channels, and give rise to fast postsynaptic responses that typically last only a few milliseconds. The latter are called metabotropic receptors, and they produce slower postsynaptic effects that may endure much longer. Abnormalities in the function of neurotransmitter systems contribute to a wide range of neurological and psychiatric disorders. As a result, many neuropharmacological therapies are based on drugs that affect neurotransmitter release, binding, and/or removal.

Categories of Neurotransmitters

More than 100 different agents are known to serve as neurotransmitters. This large number of transmitters allows for tremendous diversity in chemical signaling between neurons. It is useful to separate this panoply of transmitters into two broad categories based simply on size (Figure 6.1). **Neuropeptides** are relatively large transmitter molecules composed of 3 to 36 amino acids. Individual amino acids, such as glutamate and GABA, as well as the transmitters acetylcholine, serotonin, and histamine, are much smaller than neuropeptides and have therefore come to be called **small-molecule neurotransmitters**. Within the category of small-molecule neurotransmitters, the **biogenic amines** (dopamine, norepinephrine, epinephrine, serotonin, and histamine) are often discussed separately because of their similar chemical properties and postsynaptic actions. The particulars of synthesis, packaging, release, and removal differ for each neurotransmitter (Table 6.1). This chapter will describe some of the main features of these transmitters and their postsynaptic receptors.

Acetylcholine

As mentioned in the previous chapter, acetylcholine (ACh) was the first substance identified as a neurotransmitter. In addition to the action of ACh as the neurotransmitter at skeletal neuromuscular junctions (see Chapter 5), as well as the neuromuscular synapse between the vagus nerve and cardiac


SMALL-MOLECULE NEUROTRANSMITTERS
Acetylcholine
$(CH_3)_3\overset{+}{N}-CH_2-CH_2-O-\overset{O}{\overset{\|}{C}}-CH_3$
AMINO ACIDS
Glutamate
Aspartate
GABA
$H_3\overset{+}{N}-CH_2-CH_2-CH_2-COO^-$
Glycine
PURINES
ATP
BIOGENIC AMINES
CATECHOLAMINES
Dopamine
Norepinephrine
Epinephrine
INDOLEAMINE
Serotonin (5-HT)
IMIDAZOLEAMINE
Histamine
PEPTIDE NEUROTRANSMITTERS (more than 100 peptides, usually 3–30 amino acids long)
Example: Methionine enkephalin (Tyr–Gly–Gly–Phe–Met)
Tyr
Gly
Gly
Phe
Met

◀ **Figure 6.1** Examples of small-molecule and peptide neurotransmitters. Small-molecule transmitters can be subdivided into acetylcholine, the amino acids, purines, and biogenic amines. The catcholamines, so named because they all share the catechol moiety (i.e., a hydroxylated benzene ring), make up a distinctive subgroup within the biogenic amines. Serotonin and histamine contain an indole ring and an imidazole ring, respectively. Size differences between the small-molecule neurotransmitters and the peptide neurotransmitters are indicated by the space-filling models for glycine, norepinephrine, and methionine enkephalin. (Carbon atoms are black, nitrogen atoms blue, and oxygen atoms red.)

muscle fibers, ACh serves as a transmitter at synapses in the ganglia of the visceral motor system, and at a variety of sites within the central nervous system. Whereas a great deal is known about the function of cholinergic transmission at neuromuscular junctions and ganglionic synapses, the actions of ACh in the central nervous system are not as well understood.

Acetylcholine is synthesized in nerve terminals from the precursors acetyl coenzyme A (acetyl CoA, which is synthesized from glucose) and choline, in a reaction catalyzed by choline acetyltransferase (CAT; Figure 6.2). Choline is present in plasma at a high concentration (about 10 m*M*) and is taken up into cholinergic neurons by a high-affinity Na^+/choline transporter. After synthesis in the cytoplasm of the neuron, a vesicular ACh

TABLE 6.1
Functional Features of the Major Neurotransmitters

Neurotransmitter	*Postsynaptic effect*[a]	*Precursor(s)*	*Rate-limiting step in synthesis*	*Removal mechanism*	*Type of vesicle*
ACh	Excitatory	Choline + acetyl CoA	CAT	AChEase	Small, clear
Glutamate	Excitatory	Glutamine	Glutaminase	Transporters	Small, clear
GABA	Inhibitory	Glutamate	GAD	Transporters	Small, clear
Glycine	Inhibitory	Serine	Phosphoserine	Transporters	Small, clear
Catecholamines (epinephrine, norepinephrine, dopamine)	Excitatory	Tyrosine	Tyrosine hydroxylase	Transporters, MAO, COMT	Small dense-core, or large irregular dense-core
Serotonin (5-HT)	Excitatory	Tryptophan	Tryptophan hydroxylase	Transporters, MAO	Large, dense-core
Histamine	Excitatory	Histidine	Histidine decarboxylase	Transporters	Large, dense-core
ATP	Excitatory	ADP	Mitochondrial oxidative phosphorylation; glycolysis	Hydrolysis to AMP and adenosine	Small, clear
Neuropeptides	Excitatory and inhibitory	Amino acids (protein synthesis)	Synthesis and transport	Proteases	Large, dense-core
Endocannabinoids	Inhibits inhibition	Membrane lipids	Enzymatic modification of lipids	Hydrolasis by FAAH	None
Nitric oxide	Excitatory and inhibitory	Arginine	Nitric oxide synthase	Spontaneous oxidation	None

[a] The most common postsynaptic effect is indicated; the same transmitter can elicit postsynaptic excitation or inhibition depending on the nature of the ion channels affected by transmitter binding (see Chapter 7).

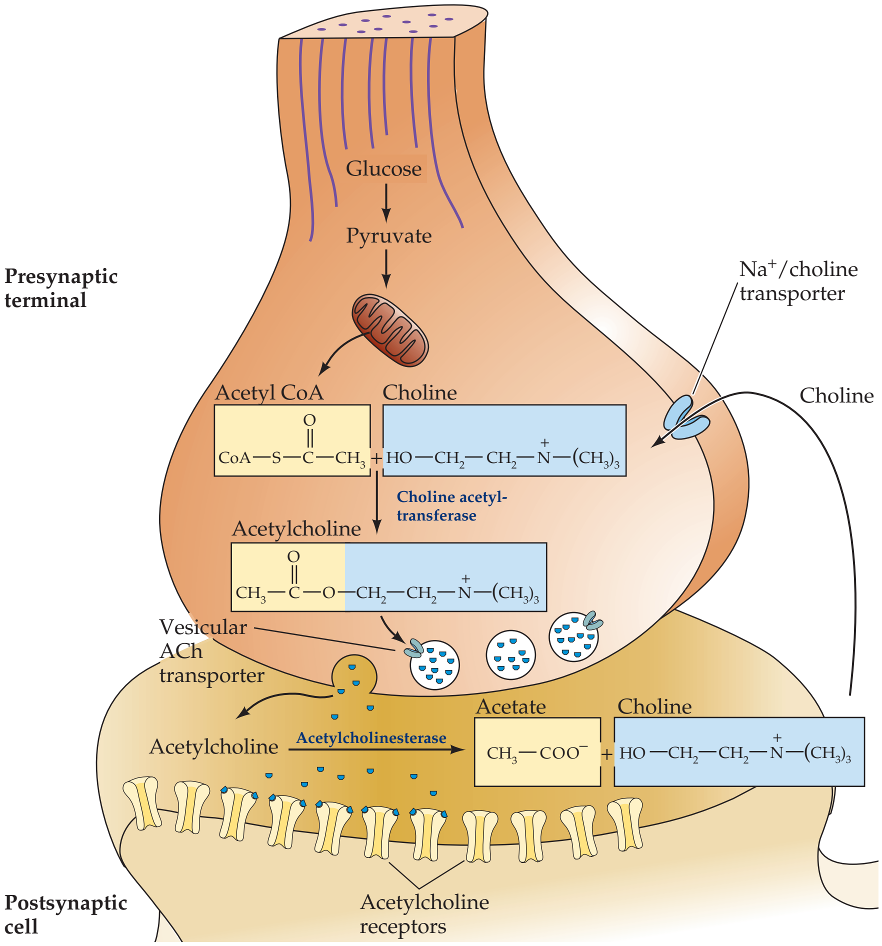

Glucose
Pyruvate
Presynaptic terminal
Na+/choline transporter
Choline
Acetyl CoA
Choline
CoA—S—C(=O)—CH3 + HO—CH2—CH2—N+—(CH3)3
Choline acetyl-transferase
Acetylcholine
CH3—C(=O)—O—CH2—CH2—N+—(CH3)3
Vesicular ACh transporter
Acetylcholine
Acetylcholinesterase
Acetate
Choline
CH3—COO− + HO—CH2—CH2—N+—(CH3)3
Postsynaptic cell
Acetylcholine receptors

Figure 6.2 Acetylcholine metabolism in cholinergic nerve terminals. The synthesis of acetylcholine from choline and acetyl CoA requires choline acetyltransferase. Acetyl CoA is derived from pyruvate generated by glycolysis, while choline is transported into the terminals via a Na^+-dependent transporter. Acetylcholine is loaded into synaptic vesicles via a vesicular transporter. After release, acetylcholine is rapidly metabolized by acetylcholinesterase, and choline is transported back into the terminal.

transporter loads approximately 10,000 molecules of ACh into each cholinergic vesicle.

In contrast to most other small-molecule neurotransmitters, the postsynaptic actions of ACh at many cholinergic synapses (the neuromuscular junction in particular) is not terminated by reuptake but by a powerful hydrolytic enzyme, acetylcholinesterase (AChE). This enzyme is concentrated in the synaptic cleft, ensuring a rapid decrease in ACh concentration after its release from the presynaptic terminal. AChE has a very high catalytic activity (about 5000 molecules of ACh per AChE molecule per second) and hydrolyzes ACh into acetate and choline. The choline produced by ACh hydrolysis is transported back into nerve terminals and used to resynthesize ACh.

Among the many interesting drugs that interact with cholinergic enzymes are the organophosphates. This group includes some potent chemical warfare agents. One such compound is the nerve gas “Sarin,” which was made notorious after a group of terrorists released this gas in Tokyo’s underground rail system. Organophosphates can be lethal because they inhibit AChE, causing ACh to accumulate at cholinergic synapses. This build-up of ACh depolarizes the postsynaptic cell and renders it refractory to subsequent ACh release, causing neuromuscular paralysis and other effects. The high sensitivity of insects to these AChE inhibitors has made organophosphates popular insecticides.

Many of the postsynaptic actions of ACh are mediated by the nicotinic ACh receptor (nAChR), so named because the CNS stimulant, nicotine, also

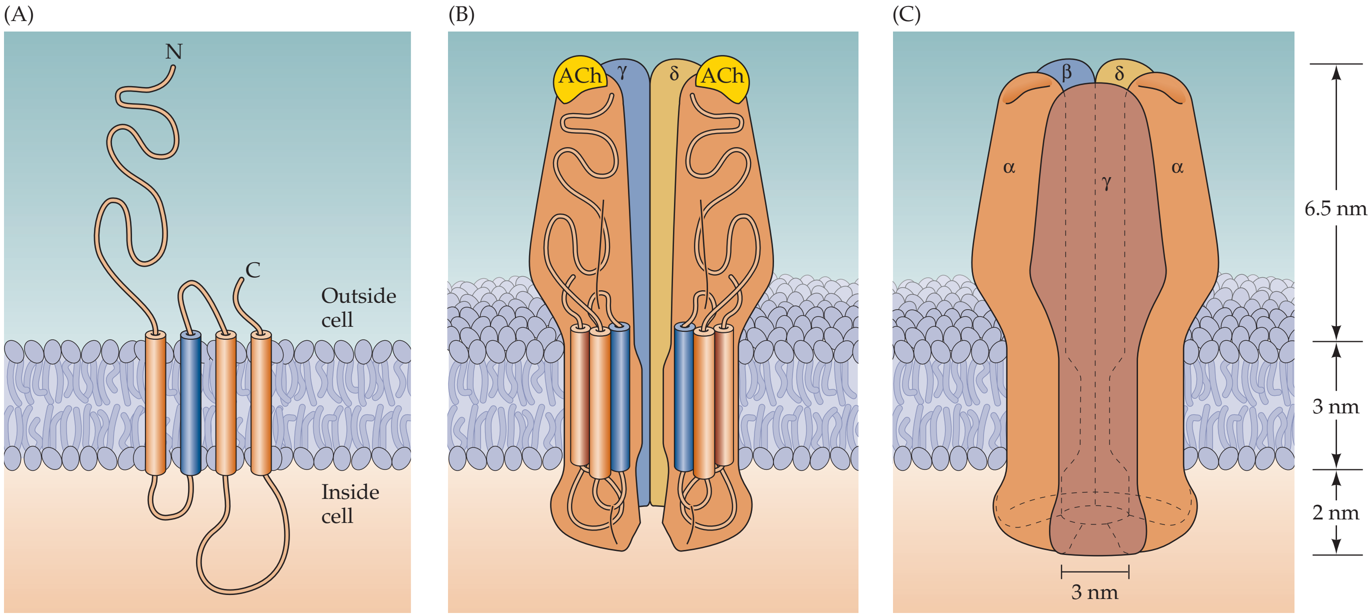
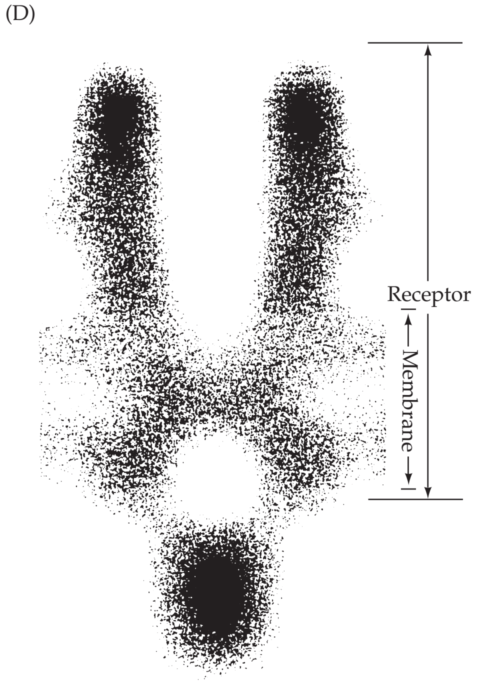


Figure 6.3 The structure of the nACh receptor/channel. (A) Each receptor subunit crosses the membrane four times. The membrane-spanning domain that lines the pore is shown in blue. (B) Five such subunits come together to form a complex structure containing 20 transmembrane domains that surround a central pore. (C) The openings at either end of the channel are very large—approximately 3 nm in diameter; even the narrowest region of the pore is approximately 0.6 nm in diameter. By comparison, the diameter of Na^+ or K^+ is less than 0.3 nm. (D) An electron micrograph of the nACh receptor, showing the actual position and size of the protein with respect to the membrane. (D from Toyoshima and Unwin, 1990.)



binds to these receptors. Nicotine consumption produces some degree of euphoria, relaxation, and eventually addiction (Box A), effects believed to be mediated in this case by nAChRs. Nicotinic receptors are the best-studied type of ionotropic neurotransmitter receptor. As described in Chapter 5, nAChRs are nonselective cation channels that generate excitatory postsynaptic responses. A number of biological toxins specifically bind to and block nicotinic receptors (Box B). The availability of these highly specific ligands—particularly a component of snake venom called α-bungarotoxin—has provided a valuable way to isolate and purify nAChRs. This pioneering work paved the way to cloning and sequencing the genes encoding the various subunits of the nAChR.

Based on these molecular studies, the nAChR is now known to be a large protein complex consisting of five subunits arranged around a central membrane-spanning pore (Figure 6.3). In the case of skeletal muscle AChRs, the receptor pentamer contains two α subunits, each of which binds one molecule of ACh. Because both ACh binding sites must be occupied for the channel to open, only relatively high concentrations of this neurotransmitter lead to channel activation. These subunits also bind other ligands, such as nicotine and α-bungarotoxin. At the neuromuscular junction, the two α subunits are combined with up to four other types of subunit—β, γ, δ, ε—in the ratio 2α:β:ε:δ. Neuronal nAChRs typically differ from those of muscle in that they lack sensitivity to α-bungaro-

Box A
Addiction

Drug addiction is a chronic, relapsing disease with obvious medical, social, and political consequences. Addiction (also called substance dependence) is a persistent disorder of brain function in which compulsive drug use occurs despite serious negative consequences for the afflicted individual. The diagnostic manual of the American Psychiatric Association defines addiction in terms of both *physical* dependence and *psychological* dependence (in which an individual continues the drug-taking behavior despite obviously maladaptive consequences).

The range of substances that can generate this sort of dependence is wide; the primary agents of abuse at present are opioids, cocaine, amphetamines, marijuana, alcohol, and nicotine. Addiction to more "socially acceptable" agents such as alcohol and nicotine are sometimes regarded as less problematic, but in fact involve medical and behavioral consequences that are at least as great as for drugs of abuse that are considered more dangerous. Importantly, the phenomenon of addiction is not limited to human behavior, but is demonstrable in laboratory animals. Most of these same agents are self-administered if primates, rodents, or other species are provided with the opportunity to do so.

In addition to a compulsion to take the agent of abuse, a major feature of addiction for many drugs is a constellation of negative physiological and emotional features, loosely referred to as "withdrawal syndrome," that occur when the drug is not taken. The signs and symptoms of withdrawal are different for each agent of abuse, but in general are characterized by effects opposite those of the positive experience induced by the drug itself. Consider, as an example, cocaine, a drug that was estimated to be in regular use by 5 to 6 million Americans during the decade of the 1990s, with about 600,000 regular users either addicted or at high risk for addiction. The positive effects of the drug smoked or inhaled as a powder in the form of the alkaloidal free base is a "high" that is nearly immediate but generally lasts only a few minutes, typically leading to a desire for additional drug in as little as 10 minutes to half an hour. The "high" is described as a feeling of well-being, self-confidence, and satisfaction. Conversely, when the drug is not available, frequent users experience depression, sleepiness, fatigue, drug-craving, and a general sense of malaise.

Another aspect of addiction to cocaine or other agents is tolerance, defined as a reduction in the response to the drug upon repeated administration. Tolerance occurs as a consequence of persistent use of a number of drugs but is particularly significant in drug addiction, since it progressively increases the dose needed to experience the desired effects.

Although it is fair to say that the neurobiology of addiction is incompletely understood, for cocaine and many other agents of abuse the addictive effects involve activation of dopamine receptors in critical brain regions involved in motivation and emotional reinforcement (see Chapter 28). The most important of these areas is the midbrain dopamine system,

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toxin, and comprise only two receptor subunit types (α and β), which are present in a ratio of 3α:2β. In all cases, however, five individual subunits assemble to form a functional, cation-selective nACh receptor.

Each subunit of the nAChR molecule contains four transmembrane domains that make up the ion channel portion of the receptor, and a long extracellular region that makes up the ACh-binding domain (Figure 6.3A). Unraveling the molecular structure of this region of the nACh receptor has provided insight into the mechanisms that allow ligand-gated ion channels to respond rapidly to neurotransmitters: The intimate association of the ACh binding sites with the pore of the channel presumably accounts for the rapid response to ACh (Figure 6.3B–D). Indeed, this general arrangement is characteristic of *all* of the ligand-gated ion channels at fast-acting synapses, as summarized in Figure 6.4. Thus, the nicotinic receptor has served as a paradigm for studies of other ligand-gated ion channels, at the same time leading to a much deeper appreciation of several neuromuscular diseases (Box C).

especially its projections from the ventral-tegmental area to the nucleus acumbens. Agents such as cocaine appear to act by raising dopamine levels in these areas, making this transmitter more available to receptors by interfering with re-uptake of synaptically released dopamine by the dopamine transporter. The reinforcement and motivation of drug-taking behaviors is thought to be related to the projections to the nucleus acumbens.

The most common opioid drug of abuse is heroin. Heroin is a derivative of the opium poppy and is not legally available for clinical purposes in the United States. The number of heroin addicts in the United States is estimated to be between 750,000 and a million individuals. The positive feelings produced by heroin, generally described as the “rush,” are often compared to the feeling of sexual orgasm and begin in less than a minute after intravenous injection. There is then a feeling of general well-being (referred to as “on the nod”) that lasts about an hour. The symptoms of withdrawal can be intense; these are restlessness, irritability, nausea, muscle pain, depression, sleeplessness, and a sense of anxiety and malaise. The reinforcing aspects of the drug entail the same dopaminergic circuitry in the ventral tegmental area and nucleus acumbens as does cocaine, although additional areas are certainly involved, particularly the sites of opioid receptors described in Chapter 9.

Interestingly, addiction to heroin or any other agent is not an inevitable consequence of drug use, but depends critically on the environment. For instance, returning veterans who were heroin addicts in Vietnam typically lost their addiction upon returning to the United States. Likewise, patients given other opioids (e.g., morphine) for painful conditions rarely become addicts.

The treatment of any form of addiction is difficult and must be tailored to the circumstances of the individual. In addition to treating acute problems of withdrawal and “detoxification,” patterns of behavior must be changed that may take months or years. Addiction is thus a chronic disease state that requires continual monitoring during the lifetime of susceptible individuals.

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A second class of ACh receptors is activated by muscarine, a poisonous alkaloid found in some mushrooms (see Box B), and thus they are referred to as muscarinic ACh receptors (mAChRs). mAChRs are metabotropic and mediate most of the effects of ACh in brain. Several subtypes of mAChR are known (Figure 6.5). Muscarinic ACh receptors are highly expressed in the striatum and various other forebrain regions, where they exert an inhibitory influence on dopamine-mediated motor effects. These receptors are also found in the ganglia of the peripheral nervous system. Finally, they mediate peripheral cholinergic responses of autonomic effector organs—such as heart, smooth muscle, and exocrine glands—and are responsible for the inhibition of heart rate by the vagus nerve. Numerous drugs act as mACh receptor agonists or antagonists, but most of these do not discriminate between different types of muscarinic receptors and often produce side effects. Nevertheless, mACh blockers that are therapeutically useful include atropine (used to dilate the pupil), scopolamine (effective in preventing motion sickness), and ipratropium (useful in the treatment of asthma).

Box B

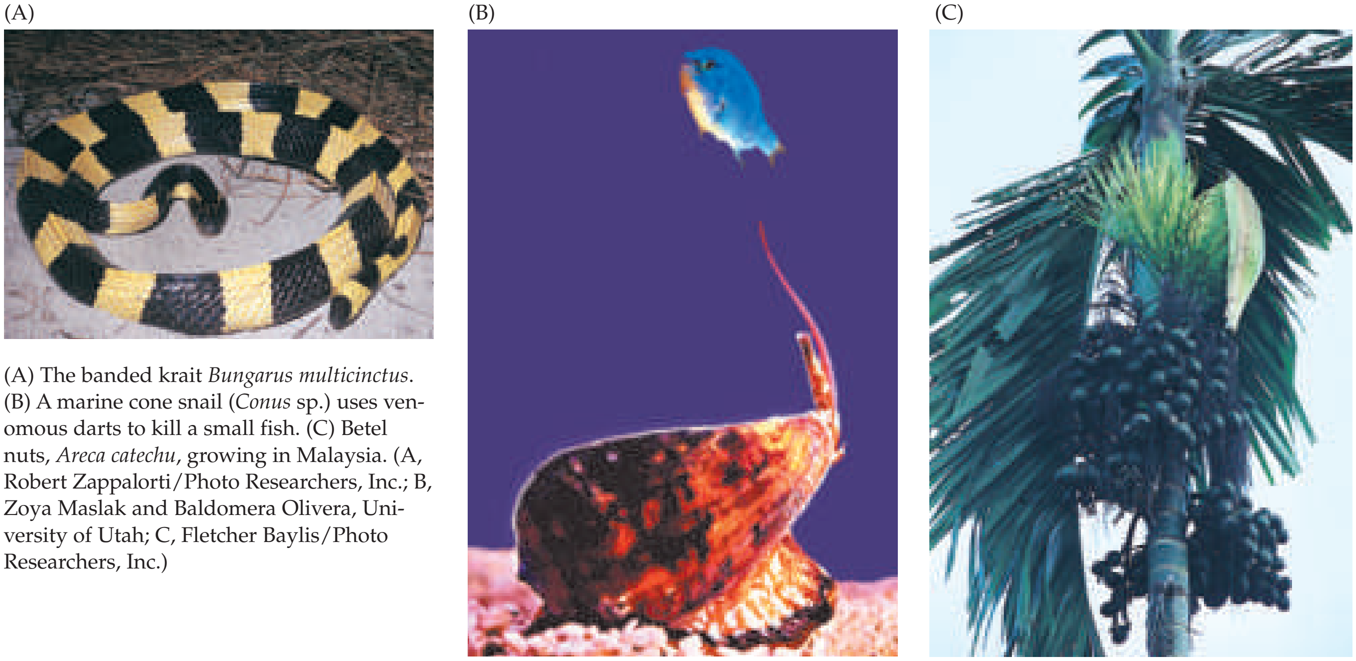
Neurotoxins that Act on Postsynaptic Receptors

Poisonous plants and venomous animals are widespread in nature. The toxins they produce have been used for a variety of purposes, including hunting, healing, mind-altering, and, more recently, research. Many of these toxins have potent actions on the nervous system, often interfering with synaptic transmission by targeting neurotransmitter receptors. The poisons found in some organisms contain a single type of toxin, whereas others contain a mixture of tens or even hundreds of toxins.

Given the central role of ACh receptors in mediating muscle contraction at neuromuscular junctions in numerous species, it is not surprising that a large number of natural toxins interfere with transmission at this synapse. In fact, the classification of nicotinic and muscarinic ACh receptors is based on the sensitivity of these receptors to the toxic plant alkaloids nicotine and muscarine, which activate nicotinic and muscarinic ACh receptors, respectively. Nicotine is derived from the dried leaves of the tobacco plant *Nicotinia tabacum*, and muscarine is from the poisonous red mushroom *Amanita muscaria*. Both toxins are stimulants that produce nausea, vomiting, mental confusion, and convulsions. Muscarine poisoning can also lead to circulatory collapse, coma, and death.

The poison α-bungarotoxin, one of many peptides that together make up the venom of the banded krait, *Bungarus multicinctus* (Figure A), blocks transmission at neuromuscular junctions and is used by the snake to paralyze its prey. This 74-amino-acid toxin blocks neuromuscular transmission by irreversibly binding to nicotinic ACh receptors, thus preventing ACh from opening postsynaptic ion channels. Paralysis ensues because skeletal muscles can no longer be activated by motor neurons. As a result of its specificity and its high affinity for nicotinic ACh receptors, α-bungarotoxin has contributed greatly to understanding the ACh receptor molecule. Other snake toxins that block nicotinic ACh receptors are cobra α-neurotoxin and the sea snake peptide erabutoxin. The same strategy used by these snakes to paralyze prey was adopted by South American Indians who used curare, a mixture of plant toxins from *Chondodendron tomentosum*, as an arrowhead poison to immobilize their quarry. Curare also blocks nicotinic ACh receptors; the active agent is the alkaloid δ-tubocurarine.

Another interesting class of animal toxins that selectively block nicotinic ACh and other receptors includes the peptides produced by fish-hunting marine cone snails (Figure B). These colorful snails kill small fish by "shooting" venomous darts into them. The venom contains hundreds of peptides, known as the conotoxins, many of which target proteins that are important in synaptic transmission. There are conotoxin peptides that block Ca^{2+} channels, Na^{+} channels, glutamate receptors, and ACh



(A) The banded krait *Bungarus multicinctus*. (B) A marine cone snail (*Conus* sp.) uses venomous darts to kill a small fish. (C) Betel nuts, *Areca catechu*, growing in Malaysia. (A, Robert Zappalorti/Photo Researchers, Inc.; B, Zoya Maslak and Baldomera Olivera, University of Utah; C, Fletcher Baylis/Photo Researchers, Inc.)

receptors. The array of physiological responses produced by these peptides all serve to immobilize any prey unfortunate enough to encounter the cone snail. Many other organisms, including other mollusks, corals, worms and frogs, also utilize toxins containing specific blockers of ACh receptors.

Other natural toxins have mind- or behavior-altering effects and in some cases have been used for thousands of years by shamans and, more recently, physicians. Two examples are plant alkaloid toxins that block muscarinic ACh receptors: atropine from deadly nightshade (belladonna), and scopolamine from henbane. Because these plants grow wild in many parts of the world, exposure is not unusual, and poisoning by either toxin can also be fatal.

Another postsynaptic neurotoxin that, like nicotine, is used as a social drug is found in the seeds from the betel nut, *Areca catechu* (Figure C). Betel nut chewing, although unknown in the United States, is practiced by up to 25% of the population in India, Bangladesh, Ceylon, Malaysia, and the Philippines. Chewing these nuts produces a euphoria caused by arecoline, an alkaloid agonist of nicotinic ACh receptors. Like nicotine, arecoline is an addictive central nervous system stimulant.

Many other neurotoxins alter transmission at noncholinergic synapses. For example, amino acids found in certain mushrooms, algae, and seeds are potent glutamate receptor agonists. The excitotoxic amino acids kainate, from the red alga *Digenea simplex*, and quisqualate, from the seed of *Quisqualis indica*, are used to distinguish two families of non-NMDA glutamate receptors (see text). Other neurotoxic amino acid activators of glutamate receptors include ibotenic acid and acromelic acid, both found in mushrooms, and domoate, which occurs in algae, seaweed, and mussels. Another large group of peptide neurotoxins blocks glutamate receptors. These include the α-agatoxins from the funnel web spider, NSTX-3 from the orb weaver spider, jorotoxin from the Joro spider, and β-philanthotoxin from wasp venom, as well as many cone snail toxins.

All the toxins discussed so far target excitatory synapses. The inhibitory GABA and glycine receptors, however, have not been overlooked by the exigencies of survival. Strychnine, an alkaloid extracted from the seeds of *Strychnos nux-vomica*, is the only drug known to have specific actions on transmission at glycinergic synapses. Because the toxin blocks glycine receptors, strychnine poisoning causes overactivity in the spinal cord and brainstem, leading to seizures. Strychnine has long been used commercially as a poison for rodents, although alternatives such as the anticoagulant coumadin are now more popular because they are safer for humans. Neurotoxins that block $\mathrm{GABA_A}$ receptors include plant alkaloids such as bicuculline from Dutchman's breeches and picrotoxin from *Anamerta cocculus*. Dieldrin, a commercial insecticide, also blocks these receptors. These agents are, like strychnine, powerful central nervous system stimulants. Muscimol, a mushroom toxin that is a powerful depressant as well as a hallucinogen, activates $\mathrm{GABA_A}$ receptors. A synthetic analogue of GABA, baclofen, is a $\mathrm{GABA_B}$ agonist that reduces EPSPs in some brainstem neurons and is used clinically to reduce the frequency and severity of muscle spasms.

Chemical warfare between species has thus given rise to a staggering array of molecules that target synapses throughout the nervous system. Although these toxins are designed to defeat normal synaptic transmission, they have also provided a set of powerful tools to understand postsynaptic mechanisms.

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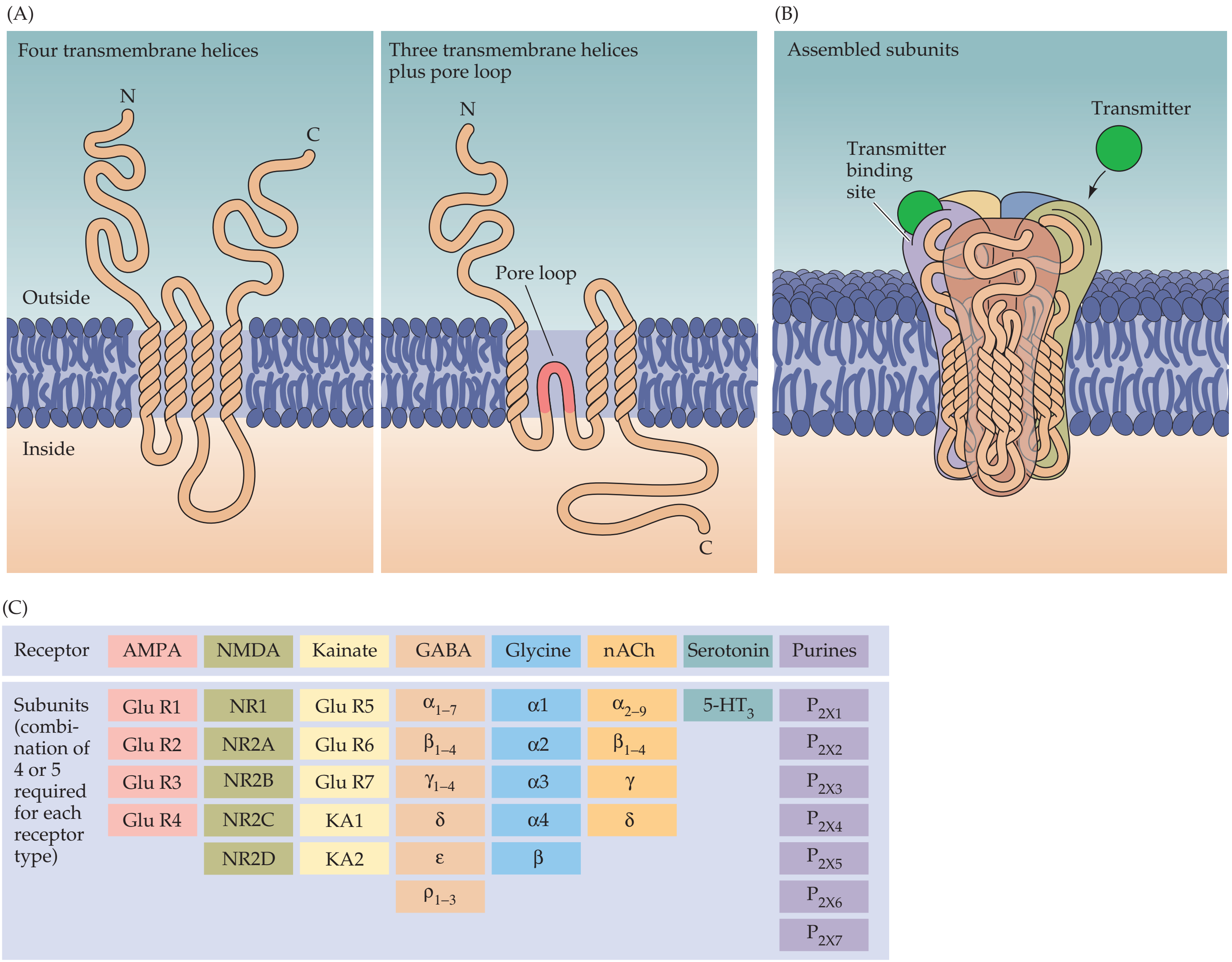
Glutamate

Glutamate is the most important transmitter in normal brain function. Nearly all excitatory neurons in the central nervous system are glutamatergic, and it is estimated that over half of all brain synapses release this agent. Glutamate plays an especially important role in clinical neurology because elevated concentrations of extracellular glutamate, released as a result of neural injury, are toxic to neurons (Box D).

Glutamate is a nonessential amino acid that does not cross the blood-brain barrier and therefore must be synthesized in neurons from local precursors. The most prevalent precursor for glutamate synthesis is glutamine, which is released by glial cells. Once released, glutamine is taken up into presynaptic



Receptor	AMPA	NMDA	Kainate	GABA	Glycine	nACh	Serotonin	Purines
Subunits (combination of 4 or 5 required for each receptor type)	Glu R1	NR1	Glu R5	α_{1-7}	α1	α_{2-9}	5-HT_3	P_{2X1}
	Glu R2	NR2A	Glu R6	β_{1-4}	α2	β_{1-4}		P_{2X2}
	Glu R3	NR2B	Glu R7	γ_{1-4}	α3	γ		P_{2X3}
	Glu R4	NR2C	KA1	δ	α4	δ		P_{2X4}
		NR2D	KA2	ε	β			P_{2X5}
				ρ_{1-3}				P_{2X6}
								P_{2X7}

Figure 6.4 The general architecture of ligand-gated receptors. (A) One of the subunits of a complete receptor. The long N-terminal region forms the ligand-binding site, while the remainder of the protein spans the membrane either four times (left) or three times (right). (B) Assembly of either four or five subunits into a complete receptor. (C) A diversity of subunits come together to form functional ionotropic neurotransmitter receptors.

terminals and metabolized to glutamate by the mitochondrial enzyme glutaminase (Figure 6.6). Glutamate can also be synthesized by transamination of 2-oxoglutarate, an intermediate of the tricarboxylic acid cycle. Hence, some of the glucose metabolized by neurons can also be used for glutamate synthesis.

The glutamate synthesized in the presynaptic cytoplasm is packaged into synaptic vesicles by transporters, termed VGLUT. At least three different VGLUT genes have been identified. Once released, glutamate is removed from the synaptic cleft by the excitatory amino acid transporters (EAATs). There are five different types of high-affinity glutamate transporters exist, some of which are present in glial cells and others in presynaptic terminals. Glutamate taken up by glial cells is converted into glutamine by the enzyme

(A)

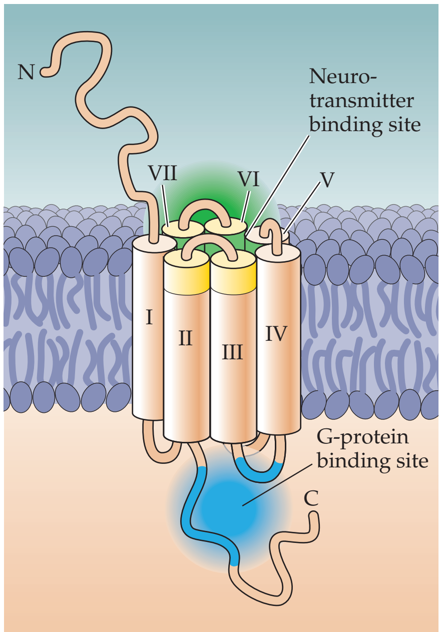
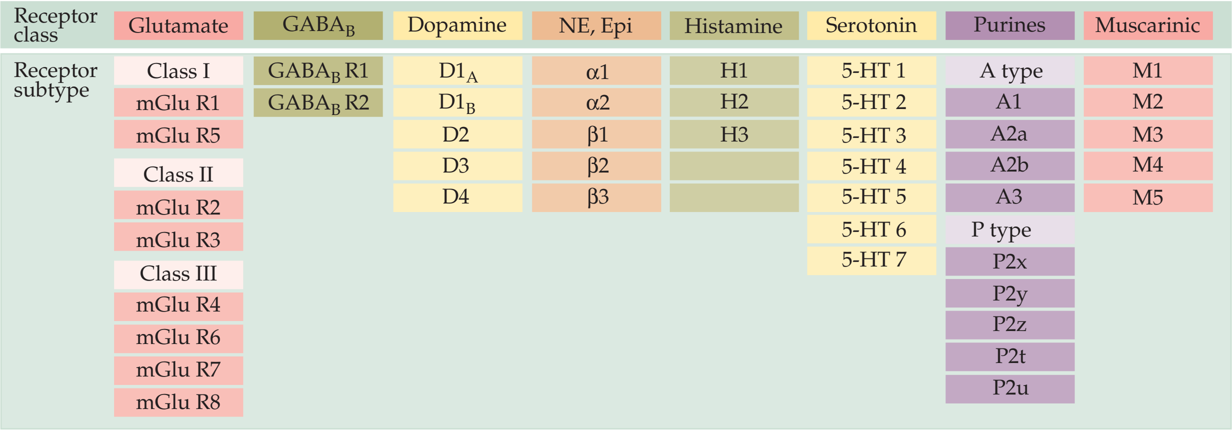


Figure 6.5 Structure and function of metabotropic receptors. (A) The transmembrane architecture of metabotropic receptors. These monomeric proteins contain seven transmembrane domains. Portions of domains II, III, VI, and VII make up the neurotransmitter-binding region. G-proteins bind to both the loop between domains V and VI and to portions of the C-terminal region. (B) Varieties of metabotropic neurotransmitter receptors.

(B)



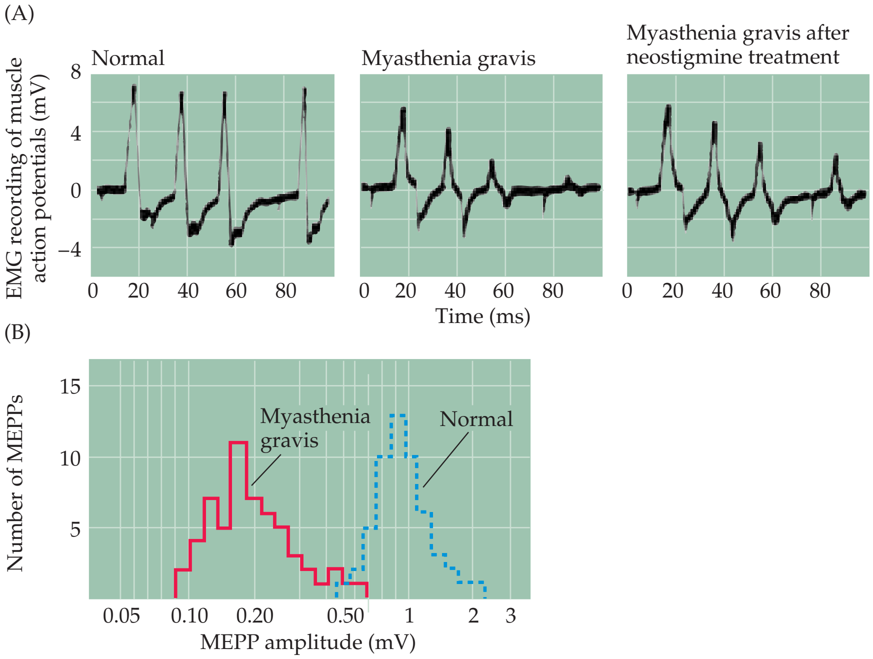
Receptor class	Glutamate	$GABA_B$	Dopamine	NE, Epi	Histamine	Serotonin	Purines	Muscarinic
Receptor subtype	Class I	$GABA_B$ R1	$D1_A$	α1	H1	5-HT 1	A type	M1
	mGlu R1	$GABA_B$ R2	$D1_B$	α2	H2	5-HT 2	A1	M2
	mGlu R5		D2	β1	H3	5-HT 3	A2a	M3
	Class II		D3	β2		5-HT 4	A2b	M4
	mGlu R2		D4	β3		5-HT 5	A3	M5
	mGlu R3					5-HT 6	P type	
	Class III					5-HT 7	P2x	
	mGlu R4						P2y	
	mGlu R6						P2z	
	mGlu R7						P2t	
	mGlu R8						P2u	

glutamine synthetase; glutamine is then transported out of the glial cells and into nerve terminals. In this way, synaptic terminals cooperate with glial cells to maintain an adequate supply of the neurotransmitter. This overall sequence of events is referred to as the **glutamate-glutamine cycle** (see Figure 6.6).

Several types of glutamate receptors have been identified. Three of these are ionotropic receptors called, respectively, **NMDA receptors, AMPA receptors, and kainate receptors** (Figure 6.4C). These glutamate receptors are named after the agonists that activate them: NMDA (*N*-methyl-D-aspartate), AMPA (α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate), and kainic acid. All of the ionotropic glutamate receptors are nonselective cation channels similar to the nAChR, allowing the passage of Na^+ and K^+, and in some cases small amounts of Ca^{2+}. Hence AMPA, kainate, and NMDA receptor activation always produces excitatory postsynaptic responses. Like other ionotropic receptors, AMPA/kainate and NMDA receptors are also formed

Box C

Myasthenia Gravis: An Autoimmune Disease of Neuromuscular Synapses



(A) Myasthenia gravis reduces the efficiency of neuromuscular transmission. Electromyographs show muscle responses elicited by stimulating motor nerves. In normal individuals, each stimulus in a train evokes the same contractile response. In contrast, transmission rapidly fatigues in myasthenic patients, although it can be partially restored by administration of acetylcholinesterase inhibitors such as neostigmine. (B) Distribution of MEPP amplitudes in muscle fibers from myasthenic patients (solid line) and controls (dashed line). The smaller size of MEPPs in myasthenics is due to a diminished number of postsynaptic receptors. (A after Harvey et al., 1941; B after Elmqvist et al., 1964.)

Myasthenia gravis is a disease that interferes with transmission between motor neurons and skeletal muscle fibers and afflicts approximately 1 of every 200,000 people. Originally described by the British physician Thomas Willis in 1685, the hallmark of the disorder is muscle weakness, particularly during sustained activity. Although the course is variable, myasthenia commonly affects muscles controlling the eyelids (resulting in drooping of the eyelids, or ptosis) and eye movements (resulting in double vision, or diplopia). Muscles controlling facial expression, chewing, swallowing, and speaking are other common targets.

An important indication of the cause of myasthenia gravis came from the clinical observation that the muscle weakness improves following treatment with inhibitors of acetylcholinesterase, the enzyme that normally degrades acetylcholine at the neuromuscular junction. Studies of muscle obtained by biopsy from myasthenic patients showed that both end plate potentials (EPPs) and miniature end plate potentials (MEPPs) are much smaller than normal (see figure; also see Chapter 5). Because both the frequency of MEPPs and the quantal content of EPPs are normal, it seemed likely that myasthenia gravis entails a disorder of the postsynaptic muscle cells. Indeed, electron microscopy shows that the structure of neuromuscular junctions is altered, obvious changes being a widening of the synaptic cleft and an apparent reduction in the number of acetylcholine receptors in the postsynaptic membrane.

A chance observation in the early 1970s led to the discovery of the underlying cause of these changes. Jim Patrick and Jon Lindstrom, then working at the Salk Institute, were attempting to raise antibodies to nicotinic acetylcholine receptors by immunizing rabbits with the receptors. Unexpectedly, the immunized rabbits developed muscle weakness that improved after treatment with acetylcholinesterase inhibitors. Subsequent work showed that the blood of myasthenic patients contains antibodies directed against the acetylcholine receptor, and that these antibodies are present at neuromuscular synapses. Removal of antibodies by plasma exchange improves the weakness. Finally, injecting the serum of myasthenic patients into mice produces myasthenic effects (because the serum carries circulating antibodies).

These findings indicate that myasthenia gravis is an autoimmune disease that targets nicotinic acetylcholine receptors. The immune response reduces the number of functional receptors at the neuromuscular junction and can eventually destroys them altogether, diminishing the efficiency of synaptic transmission; muscle weakness thus occurs because motor neurons are less capable of exciting the postsynaptic muscle cells. This causal sequence also explains why cholinesterase inhibitors alleviate the signs and symptoms of myasthenia: The inhibitors increase the concentration of acetylcholine in the synaptic cleft, allowing more effective activation of those postsynaptic receptors not yet destroyed by the immune system.

Despite all these insights, it is still not clear what triggers the immune system to produce an autoimmune response to acetylcholine receptors. Surgical removal of the thymus is beneficial in young patients with hyperplasia of the thymus, though precisely how the thymus contributes to myasthenia gravis is incompletely understood. Many patients are treated with combinations of immunosuppression and cholinesterase inhibitors.

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from the association of several protein subunits that can combine in many ways to produce a large number of receptor isoforms (see Figure 6.4C).

NMDA receptors have especially interesting properties (Figure 6.7A). Perhaps most significant is the fact that NMDA receptor ion channels allow the entry of Ca^{2+} in addition to monovalent cations such as Na^+ and K^+. As a result, EPSPs produced by NMDA receptors can increase the concentration of Ca^{2+} within the postsynaptic neuron; the Ca^{2+} concentration change can then act as a second messenger to activate intracellular signaling cascades (see Chapter 7). Another key property is that they bind extracellular Mg^{2+}. At hyperpolarized membrane potentials, this ion blocks the pore of the NMDA receptor channel. Depolarization, however, pushes Mg^{2+} out of the pore, allowing other cations to flow. This property provides the basis for a voltage-dependence to current flow through the receptor (dashed line in Figure 6.7B) and means that NMDA receptors pass cations (most notably Ca^{2+})

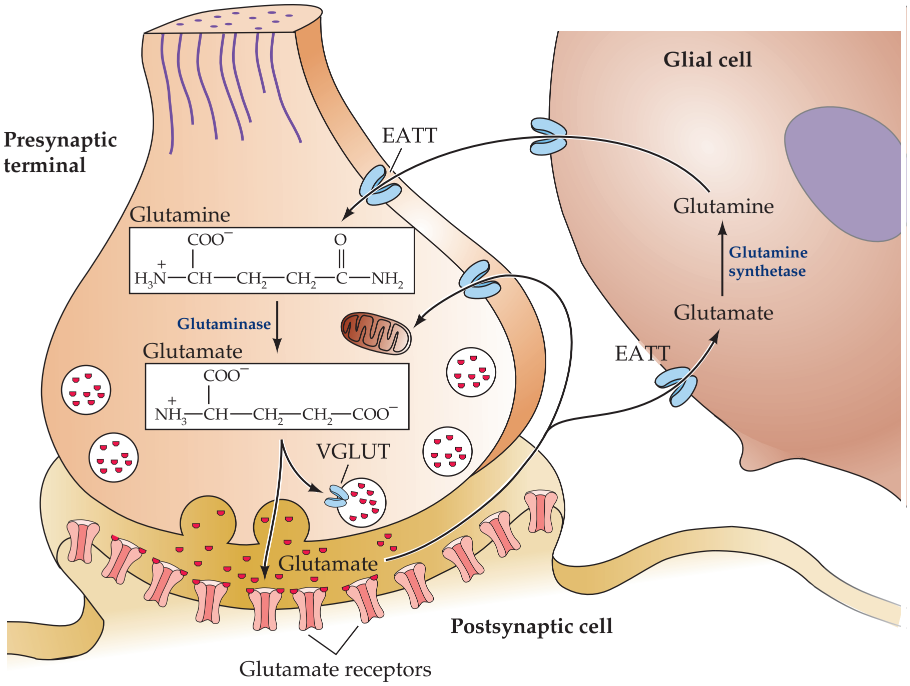


Figure 6.6 Glutamate synthesis and cycling between neurons and glia. The action of glutamate released into the synaptic cleft is terminated by uptake into neurons and surrounding glial cells via specific transporters. Within the nerve terminal, the glutamine released by glial cells and taken up by neurons is converted back to glutamate. Glutamate is transported into cells via excitatory amino acid transporters (EATTs) and loaded into synaptic vesicles via vesicular glutamate transporters (VGLUT).

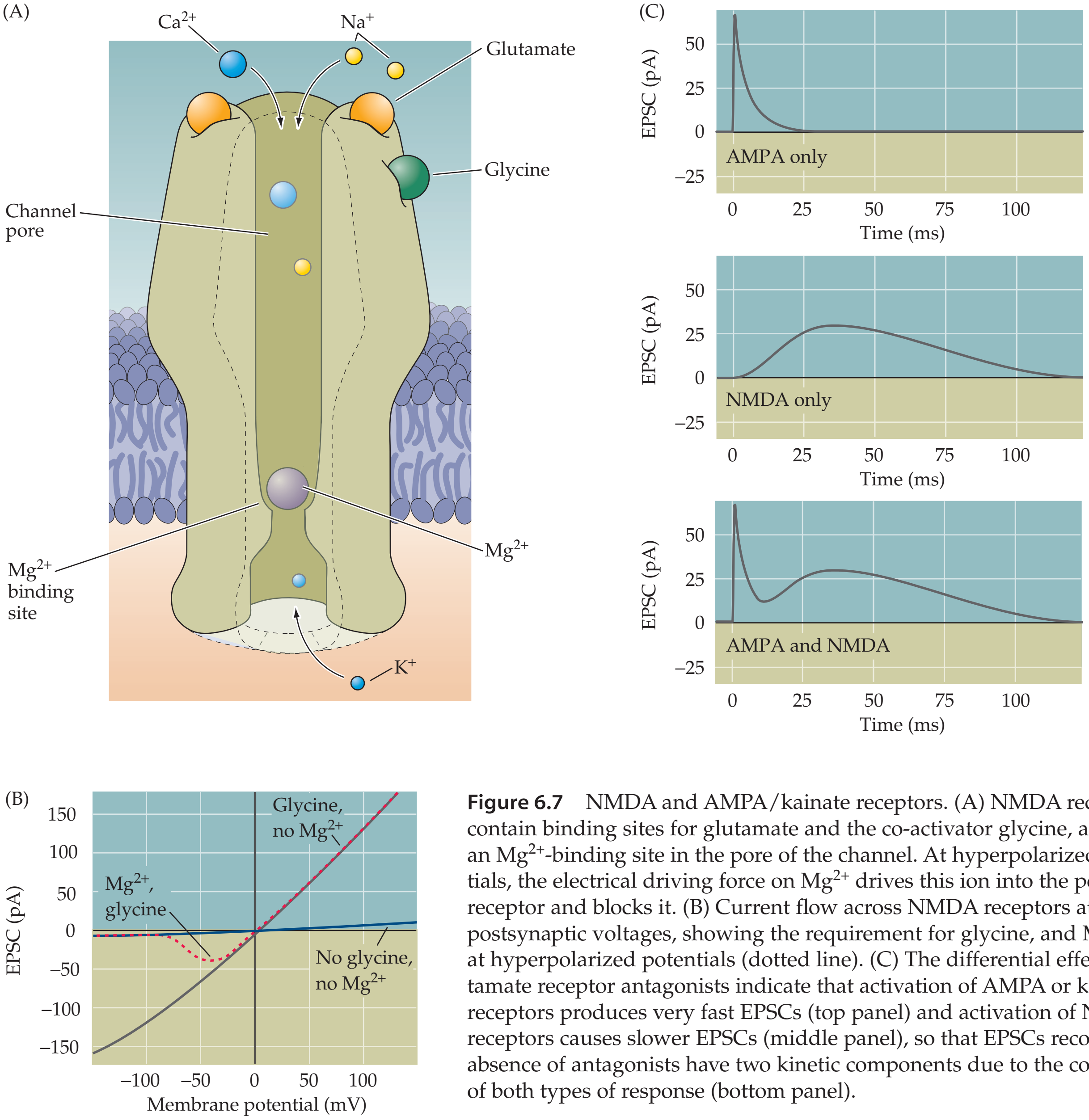

(A)
Ca2+
Na+
Glutamate
Glycine
Channel pore
Mg2+ binding site
Mg2+
K+
(C)
EPSC (pA)
50
25
0
–25
AMPA only
0 25 50 75 100
Time (ms)
NMDA only
AMPA and NMDA
(B)
EPSC (pA)
150
100
50
0
–50
–100
–150
Glycine, no Mg2+
Mg2+, glycine
No glycine, no Mg2+
–100 –50 0 50 100
Membrane potential (mV)

Figure 6.7 NMDA and AMPA/kainate receptors. (A) NMDA receptors contain binding sites for glutamate and the co-activator glycine, as well as an Mg^{2+}-binding site in the pore of the channel. At hyperpolarized potentials, the electrical driving force on Mg^{2+} drives this ion into the pore of the receptor and blocks it. (B) Current flow across NMDA receptors at a range of postsynaptic voltages, showing the requirement for glycine, and Mg^{2+} block at hyperpolarized potentials (dotted line). (C) The differential effects of glutamate receptor antagonists indicate that activation of AMPA or kainate receptors produces very fast EPSCs (top panel) and activation of NMDA receptors causes slower EPSCs (middle panel), so that EPSCs recorded in the absence of antagonists have two kinetic components due to the contribution of both types of response (bottom panel).

only during depolarization of the postsynaptic cell, due to either activation of a large number of excitatory inputs and/or by repetitive firing of action potentials in the presynaptic cell. These properties are widely thought to be the basis for some forms of information storage at synapses, such as memory, as described in Chapter 24. Another unusual property of NMRA receptors is that opening the channel of this receptor requires the presence of a co-agonist, the amino acid glycine (Figure 6.7A,B). There are at least five forms of NMDA receptor subunits (NMDA-R1, and NMDA-R2A through NMDA-R2D); different synapses have distinct combinations of these subunits, producing a variety of NMDA receptor-mediated postsynaptic responses.

Whereas some glutamatergic synapses have only AMPA or NMDA receptors, most possess both AMPA and NMDA receptors. An antagonist of

NMDA receptors, APV (2-amino-5-phosphono-valerate), is often used to differentiate between the two receptor types. The use of this drug has also revealed differences between the EPSPs produced by NMDA and those produced by AMPA/kainate receptors, such as the fact that the synaptic currents produced by NMDA receptors are slower and longer-lasting than the those produced by AMPA/kainate receptors (see Figure 6.7C).

In addition to these ionotropic glutamate receptors, there are three types of metabotropic glutamate receptor (mGluRs) (Figure 6.5). These receptors, which modulate postsynaptic ion channels indirectly, differ in their coupling to intracellular signal transduction pathways (see Chapter 7) and in their sensitivity to pharmacological agents. Activation of many of these receptors leads to inhibition of postsynaptic Ca^{2+} and Na^{+} channels. Unlike the excitatory ionotropic glutamate receptors, mGluRs cause slower postsynaptic responses that can either increase or decrease the excitability of postsynaptic cells. As a result the physiological roles of mGluRs are quite varied.

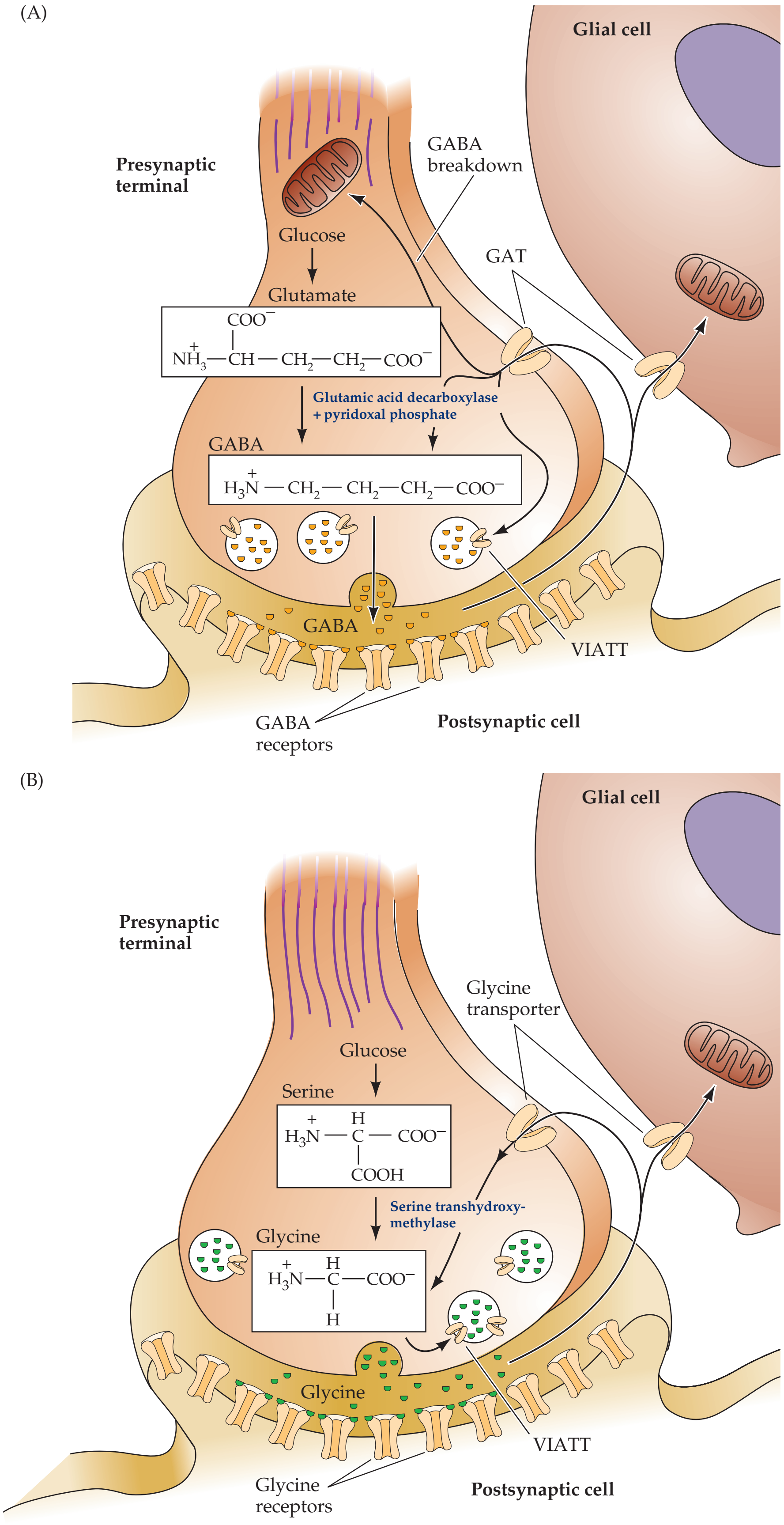
GABA and Glycine

Most inhibitory synapses in the brain and spinal cord use either γ-aminobutyric acid (GABA) or glycine as neurotransmitters. Like glutamate, GABA was identified in brain tissue during the 1950s. The details of its synthesis and degradation were worked out shortly thereafter by the work of Ernst Florey and Eugene Roberts. During this era, David Curtis and Jeffrey Watkins first showed that GABA can inhibit action potential firing in mammalian neurons. Subsequent studies by Edward Kravitz and colleagues established that GABA serves as an inhibitory transmitter at lobster neuromuscular synapses. It is now known that as many as a third of the synapses in the brain use GABA as their inhibitory neurotransmitter. GABA is most commonly found in local circuit interneurons, although cerebellar Purkinje cells provide an example of a GABAergic projection neuron (see Chapter 18).

The predominant precursor for GABA synthesis is glucose, which is metabolized to glutamate by the tricarboxylic acid cycle enzymes (pyruvate and glutamine can also act as precursors). The enzyme glutamic acid decarboxylase (GAD), which is found almost exclusively in GABAergic neurons, catalyzes the conversion of glutamate to GABA (Figure 6.8A). GAD requires a cofactor, pyridoxal phosphate, for activity. Because pyridoxal phosphate is derived from vitamin B_6, a B_6 deficiency can lead to diminished GABA synthesis. The significance of this became clear after a disastrous series of infant deaths was linked to the omission of vitamin B_6 from infant formula. This lack of B_6 resulted in a large reduction in the GABA content of the brain, and the subsequent loss of synaptic inhibition caused seizures that in some cases were fatal. Once GABA is synthesized, it is transported into synaptic vesicles via a vesicular inhibitory amino acid transporter (VIATT).

The mechanism of GABA removal is similar to that for glutamate: Both neurons and glia contain high-affinity transporters for GABA, termed GATs (several forms of GAT have been identified). Most GABA is eventually converted to succinate, which is metabolized further in the tricarboxylic acid cycle that mediates cellular ATP synthesis. The enzymes required for this degradation, GABA transaminase and succinic semialdehyde dehydrogenase, are mitochondrial enzymes. Inhibition of GABA breakdown causes a rise in tissue GABA content and an increase in the activity of inhibitory neurons. There are also other pathways for degradation of GABA. The most noteworthy of these results in the production of γ-hydroxybutyrate, a GABA derivitive that has been abused as a “date rape” drug. Oral adminis-

Figure 6.8 Synthesis, release, and reuptake of the inhibitory neurotransmitters GABA and glycine. (A) GABA is synthesized from glutamate by the enzyme glutamic acid decarboxylase, which requires pyridoxal phosphate. (B) Glycine can be synthesized by a number of metabolic pathways; in the brain, the major precursor is serine. High-affinity transporters terminate the actions of these transmitters and return GABA or glycine to the synaptic terminals for reuse, with both transmitters being loaded into synaptic vesicles via the vesicular inhibitory amino acid transporter (VIATT).


(A)
Glial cell
Presynaptic terminal
GABA breakdown
Glucose
GAT
Glutamate
COO^-
$\overset{+}{N}H_3-CH-CH_2-CH_2-COO^-$
Glutamic acid decarboxylase + pyridoxal phosphate
GABA
$H_3\overset{+}{N}-CH_2-CH_2-CH_2-COO^-$
GABA
VIATT
GABA receptors
Postsynaptic cell
(B)
Glial cell
Presynaptic terminal
Glycine transporter
Glucose
Serine
H
$H_3\overset{+}{N}-C-COO^-$
COOH
Serine transhydroxymethylase
Glycine
H
$H_3\overset{+}{N}-C-COO^-$
H
Glycine
VIATT
Glycine receptors
Postsynaptic cell

Box D

Excitotoxicity Following Acute Brain Injury

Excitotoxicity refers to the ability of glutamate and related compounds to destroy neurons by prolonged excitatory synaptic transmission. Normally, the concentration of glutamate released into the synaptic cleft rises to high levels (approximately 1 m*M*), but it remains at this concentration for only a few milliseconds. If abnormally high levels of glutamate accumulate in the cleft, the excessive activation of neuronal glutamate receptors can literally excite neurons to death.

The phenomenon of excitotoxicity was discovered in 1957 when D. R. Lucas and J. P. Newhouse serendipitously found that feeding sodium glutamate to infant mice destroys neurons in the retina. Roughly a decade later, John Olney at Washington University extended this discovery by showing that regions of glutamate-induced neuronal loss can occur throughout the brain. The damage was evidently restricted to the postsynaptic cells—the dendrites of the target neurons were grossly swollen—while the presynaptic terminals were spared. Olney also examined the relative potency of glutamate analogs and found that their neurotoxic actions paralleled their ability to activate postsynaptic glutamate receptors. Furthermore, glutamate receptor antagonists were effective in blocking the neurotoxic effects of glutamate. In light of this evidence, Olney postulated that glutamate destroys neurons by a mechanism similar to transmission at excitatory glutamatergic synapses, and coined the term *excitotoxic* to refer to this pathological effect.

Evidence that excitotoxicity is an important cause of neuronal damage after brain injury has come primarily from studying the consequences of reduced blood flow. The most common cause of reduced blood flow to the brain (ischemia) is the occlusion of a cerebral blood vessel (i.e., a stroke; see Appendix 3). The idea that excessive synaptic activity contributes to ischemic injury emerged from the observation that concentrations of glutamate and aspartate in the extracellular space around neurons increase during ischemia. Moreover, microinjection of glutamate receptor antagonists in experimental animals protects neurons from ischemia-induced damage. Together, these findings imply that extracellular accumulation of glutamate during ischemia activates glutamate receptors excessively, and that this somehow triggers a chain of events that leads to neuronal death. The reduced supply of oxygen and glucose presumably elevates extracellular glutamate levels by slowing the energy-dependent removal of glutamate at synapses.

Excitotoxic mechanisms have now been shown to be involved in other acute forms of neuronal insult, including hypoglycemia, trauma, and repeated intense seizures (called status epilepticus). Understanding excitotoxicity therefore has important implications for treating a variety of neurological disorders. For instance, a blockade of glutamate receptors could, in principle, protect neurons from injury due to stroke, trauma, or other causes. Unfortunately, clinical trials of glutamate receptor antagonists have not led to much improvement in the outcome of stroke. The ineffectiveness of this quite logical treatment is probably due to several factors, one of which is that substantial excitotoxic injury occurs quite soon after ischemia, prior to the typical initiation of treatment. It is also likely that excitotoxicity is only one of several mechanisms by which ischemia damages neurons, other candidates including damage secondary to inflammation. Pharmacological interventions that target all these mechanisms nonetheless hold considerable promise for minimizing brain injury after stroke and other causes.

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tration of γ-hydroxybutyrate can cause euphoria, memory deficits, and unconsciousness. Presumably these effects arise from actions on GABAergic synapses in the CNS.

Inhibitory synapses employing GABA as their transmitter can exhibit three types of postsynaptic receptors, called $GABA_A$, $GABA_B$, and $GABA_C$. $GABA_A$ and $GABA_C$ receptors are ionotropic receptors, while $GABA_B$ receptors are metabotropic. The ionotropic GABA receptors are usually inhibitory because their associated channels are permeable to Cl^- (Figure 6.9A); the flow of the negatively charged chloride ions inhibits postsynaptic cells since the reversal potential for Cl^- is more negative than the threshold for neuronal firing (see Figure 5.19B). Like other ionotropic receptors, GABA receptors are pentamers assembled from a combination of five types of subunits (α, β, γ, δ, and ρ; see Figure 6.4C). As a result of this subunit diversity, as well as variable stoichiometry of subunits, the function of GABA$_A$ receptors differs widely among neuronal types. Drugs that act as agonists or modulators of postsynaptic GABA receptors, such as benzodiazepines and barbiturates, are used clinically to treat epilepsy and are effective sedatives and anesthetics. Binding sites for GABA, barbiturates, steroids, and picrotoxin are all located within the pore domain of the channel (Figure 6.9B). Another site, called the benzodiazepine binding site, lies outside the pore and modulates channel activity. Benzodiazepines, such as diazepam (Valium®) and chlordiazepoxide (Librium®), are tranquilizing (anxiety reducing) drugs that enhance GABAergic transmission by binding to the α and δ subunits of GABA$_A$ receptors. Barbiturates, such as phenobarbital and pentobarbital, are hypnotics that bind to the α and β subunits of some GABA receptors and are used therapeutically for anesthesia and to control epilepsy. Another drug that can alter the activity of GABA-mediated inhibitory circuits is alcohol; at least some aspects of drunken behavior are caused by the alcohol-mediated alterations in ionotropic GABA receptors.

Metabotropic GABA receptors (GABA$_B$) are also widely distributed in brain. Like the ionotropic GABA$_A$ receptors, GABA$_B$ receptors are inhibitory. Rather than activating Cl^- selective channels, however, GABA$_B$-mediated inhibition is due to the activation of K^+ channels. A second mechanism for

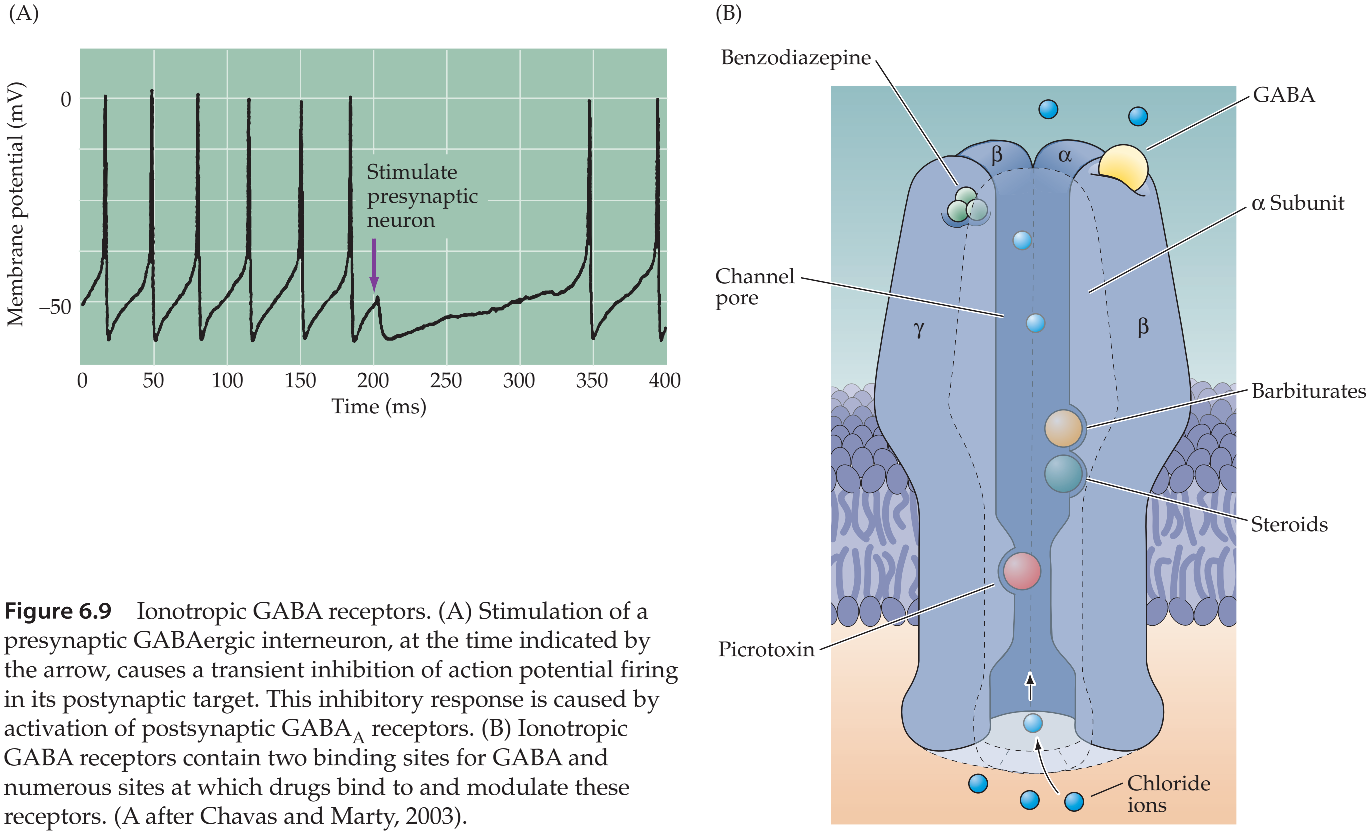

Figure 6.9 Ionotropic GABA receptors. (A) Stimulation of a presynaptic GABAergic interneuron, at the time indicated by the arrow, causes a transient inhibition of action potential firing in its postynaptic target. This inhibitory response is caused by activation of postsynaptic GABA$_A$ receptors. (B) Ionotropic GABA receptors contain two binding sites for GABA and numerous sites at which drugs bind to and modulate these receptors. (A after Chavas and Marty, 2003).

$GABA_B$-mediated inhibition is by blocking Ca^{2+} channels, which tends to hyperpolarize postsynaptic cells. Unlike most metabotropic receptors, $GABA_B$ receptors appear to assemble as heterodimers of $GABA_B$ R1 and R2 subunits.

The distribution of the neutral amino acid glycine in the central nervous system is more localized than that of GABA. About half of the inhibitory synapses in the spinal cord use glycine; most other inhibitory synapses use GABA. Glycine is synthesized from serine by the mitochondrial isoform of serine hydroxymethyltransferase (Figure 6.8B), and is transported into synaptic vesicles via the same vesicular inhibitory amino acid transporter that loads GABA into vesicles. Once released from the presynaptic cell, glycine is rapidly removed from the synaptic cleft by the plasma membrane glycine transporters. Mutations in the genes coding for some of these enzymes result in hyperglycinemia, a devastating neonatal disease characterized by lethargy, seizures, and mental retardation.

The receptors for glycine are also ligand-gated Cl^- channels, their general structure mirroring that of the $GABA_A$ receptors. Glycine receptors are pentamers consisting of mixtures of the 4 gene products encoding glycine-binding α subunits, along with the accessory β subunit. Glycine receptors are potently blocked by strychnine, which may account for the toxic properties of this plant alkaloid (see Box B).

The Biogenic Amines

Biogenic amine transmitters regulate many brain functions and are also active in the peripheral nervous system. Because biogenic amines are implicated in such a wide range of behaviors (ranging from central homeostatic functions to cognitive phenomena such as attention), it is not surprising that defects in biogenic amines function are implicated in most psychiatric disorders. The pharmacology of amine synapses is critically important in psychotherapy, with drugs affecting the synthesis, receptor binding, or catabolism of these neurotransmitters being among the most important agents in the armamentarium of modern pharmacology (Box E). Many drugs of abuse also act on biogenic amine pathways.

There are five well-established biogenic amine neurotransmitters: the three **catecholamines—dopamine, norepinephrine** (**noradrenaline**), and **epinephrine** (**adrenaline**)—and **histamine** and **serotonin** (see Figure 6.1). All the catecholamines (so named because they share the catechol moiety) are derived from a common precursor, the amino acid tyrosine (Figure 6.10). The first step in catecholamine synthesis is catalyzed by tyrosine hydroxylase in a reaction requiring oxygen as a co-substrate and tetrahydrobiopterin as a cofactor to synthesize dihydroxyphenylalanine (DOPA). Histamine and serotonin are synthesized via other routes, as described below.

- *Dopamine* is present in several brain regions (Figure 6.11A), although the major dopamine-containing area of the brain is the corpus striatum, which receives major input from the substantia nigra and plays an essential role in the coordination of body movements. In Parkinson's disease, for instance, the dopaminergic neurons of the substantia nigra degenerate, leading to a characteristic motor dysfunction (see Box B in Chapter 17). Dopamine is also believed to be involved in motivation, reward, and reinforcement, and many drugs of abuse work by affecting dopaminergic synapses in the CNS (see Box A). In addition to these roles in the CNS, dopamine also plays a poorly understood role in some sympathetic ganglia.

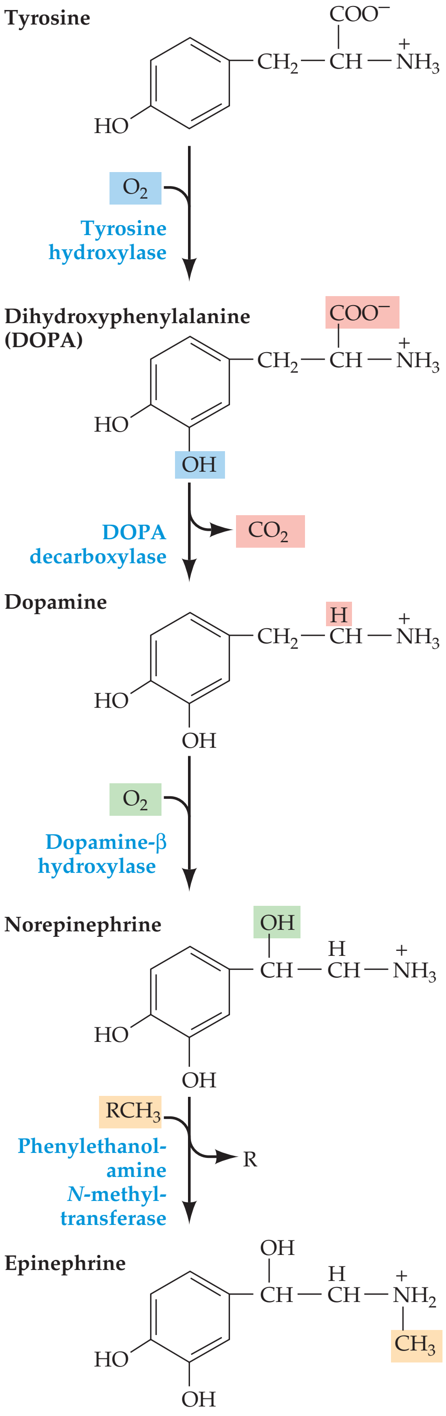

Figure 6.10 The biosynthetic pathway for the catecholamine neurotransmitters. The amino acid tyrosine is the precursor for all three catecholamines. The first step in this reaction pathway, catalyzed by tyrosine hydroxylase, is rate-limiting.

Box E

Biogenic Amine Neurotransmitters and Psychiatric Disorders

The regulation of the biogenic amine neurotransmitters is altered in a variety of psychiatric disorders. Indeed, most psychotropic drugs (defined as drugs that alter behavior, mood, or perception) selectively affect one or more steps in the synthesis, packaging, or degradation of biogenic amines. Sorting out how these drugs work has been extremely useful in beginning to understand the molecular mechanisms underlying some of these diseases.

Based on their effects on humans, psychotherapeutic drugs can be divided into several broad categories: antipsychotics, antianxiety drugs, antidepressants, and stimulants. The first antipsychotic drug used to ameliorate disorders such as schizophrenia was reserpine. Reserpine was developed in the 1950s and initially used as an antihypertensive agent; it blocks the uptake of norepinephrine into synaptic vesicles and therefore depletes the transmitter at aminergic terminals, diminishing the ability of the sympathetic division of the visceral motor system to cause vasoconstriction (see Chapter 20). A major side effect in hypertensive patients treated with reserpine—behavioral depression—suggested the possibility of using it as an antipsychotic agent in patients suffering from agitation and pathological anxiety. (Its ability to cause depression in mentally healthy individuals also suggested that aminergic transmitters are involved in mood disorders; see Box E in Chapter 28.)

Although reserpine is no longer used as an antipsychotic agent, its initial success stimulated the development of antipsychotic drugs such as chlorpromazine, haloperidol, and benperidol, which over the last several decades have radically changed the approach to treating psychotic disorders. Prior to the discovery of these drugs, psychotic patients were typically hospitalized for long periods, sometimes indefinitely, and in the 1940s were subjected to desperate measures such as frontal lobotomy (see Box B in Chapter 25). Modern antipsychotic drugs now allow most patients to be treated on an outpatient basis after a brief hospital stay. Importantly, the clinical effectiveness of these drugs is correlated with their ability to block brain dopamine receptors, implying that activation of dopamine receptors contributes to some types of psychotic illness. A great deal of effort continues to be expended on developing more effective antipsychotic drugs with fewer side effects, and on discovering the mechanism and site of action of these medications.

The second category of psychotherapeutic drugs is the antianxiety agents. Anxiety disorders are estimated to afflict 10–35% of the population, making them the most common psychiatric problem. The two major forms of pathological anxiety—panic attacks and generalized anxiety disorder—both respond to drugs that affect aminergic transmission. The agents used to treat panic disorders include inhibitors of the enzyme monoamine oxidase (MAO inhibitors) required for the catabolism of the amine neurotransmitters, and blockers of serotonin receptors. The most effective drugs in treating generalized anxiety disorder have been benzodiazepines, such as chlordiazepoxide (Librium®), and diazepam (Valium®). In contrast to most other psychotherapeutic drugs, these agents increase the efficacy of transmission at GABA_A synapses rather than acting at aminergic synapses.

Antidepressants and stimulants also affect aminergic transmission. A large number of drugs are used clinically to treat depressive disorders. The three major classes of antidepressants—MAO inhibitors, tricyclic antidepressants, and serotonin uptake blockers such as fluoxetine (Prozac®) and trazodone—all influence various aspects of aminergic transmission. MAO inhibitors such as phenelzine block the breakdown of amines, whereas the tricyclic antidepressants such as desipramine block the reuptake of norepinephrine and other amines. The extraordinarily popular antidepressant fluoxetine (Prozac®) selectively blocks the reuptake of serotonin without affecting the reuptake of catecholamines. Stimulants such as amphetamine are also used to treat some depressive disorders. Amphetamine stimulates the release of norepinephrine from nerve terminals; the transient "high" resulting from taking amphetamine may reflect the emotional opposite of the depression that sometimes follows reserpine-induced norepinephrine depletion.

Despite the relatively small number of aminergic neurons in the brain, this litany of pharmacological actions emphasizes that these neurons are critically important in the maintenance of mental health.

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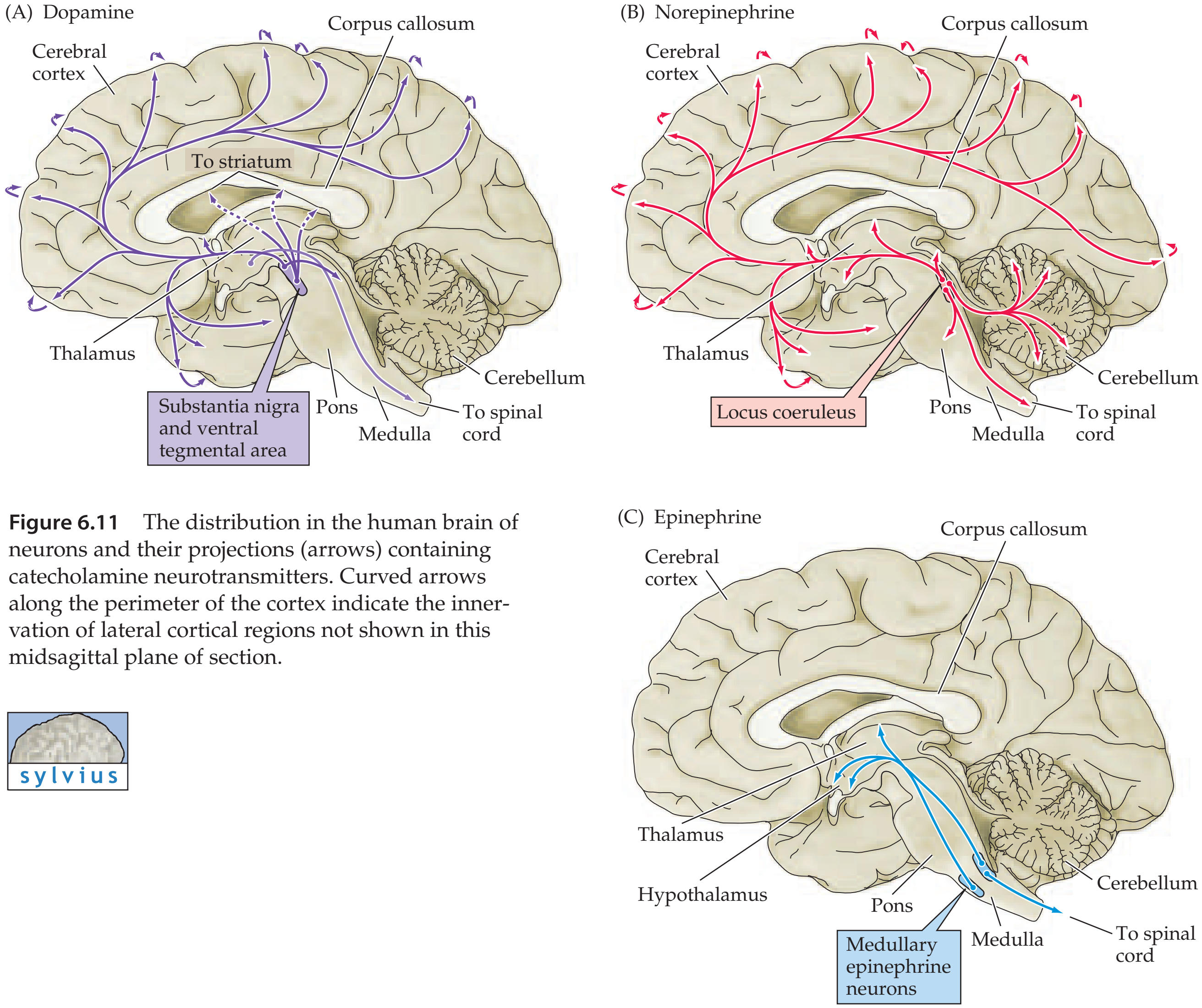

(A) Dopamine
Cerebral cortex
Corpus callosum
To striatum
Thalamus
Substantia nigra and ventral tegmental area
Pons
Medulla
Cerebellum
To spinal cord
(B) Norepinephrine
Cerebral cortex
Corpus callosum
Thalamus
Locus coeruleus
Pons
Medulla
Cerebellum
To spinal cord
(C) Epinephrine
Cerebral cortex
Corpus callosum
Thalamus
Hypothalamus
Pons
Medullary epinephrine neurons
Medulla
Cerebellum
To spinal cord

Figure 6.11 The distribution in the human brain of neurons and their projections (arrows) containing catecholamine neurotransmitters. Curved arrows along the perimeter of the cortex indicate the innervation of lateral cortical regions not shown in this midsagittal plane of section.

sylvius

Dopamine is produced by the action of DOPA decarboxylase on DOPA (see Figure 6.10). Following its synthesis in the cytoplasm of presynaptic terminals, dopamine is loaded into synaptic vesicles via a vesicular monoamine transporter (VMAT). Dopamine action in the synaptic cleft is terminated by reuptake of dopamine into nerve terminals or surrounding glial cells by a Na$^+$-dependent dopamine transporter, termed DAT. Cocaine apparently produces its psychotropic effects by binding to and inhibiting DAT, yielding a net increase in dopamine release from specific brain areas. Amphetamine, another addictive drug, also inhibits DAT as well as the transporter for norepinepherine (see below). The two major enzymes involved in the catabolism of dopamine are monoamine oxidase (MAO) and catechol *O*-methyltransferase (COMT). Both neurons and glia contain mitochondrial MAO and cytoplasmic COMT. Inhibitors of these enzymes, such as phenelzine and tranylcypromine, are used clinically as antidepressants (see Box E).

Once released, dopamine acts exclusively by activating G-protein-coupled receptors. These are mainly dopamine-specific receptors, although β-adrenergic receptors also serve as important targets of norepinepherine and epinepherine (see below). Most dopamine receptor subtypes (see Figure 6.5B) act by either activating or inhibiting adenylyl cyclase (see Chapter 7). Activation of these receptors generally contribute to complex behaviors; for example, administration of dopamine receptor agonists elicits hyperactivity and repetitive, stereotyped behavior in laboratory animals. Activation of another type of dopamine receptor in the medulla inhibits vomiting. Thus, antagonists of these receptors are used as emetics to induce vomiting after poisoning or a drug overdose. Dopamine receptor antagonists can also elicit catalepsy, a state in which it is difficult to initiate voluntary motor movement, suggesting a basis for this aspect of some psychoses.

- *Norepinephrine* (also called noradrenaline) is used as a neurotransmitter in the locus coeruleus, a brainstem nucleus that projects diffusely to a variety of forebrain targets (Figure 6.11B) and influences sleep and wakefulness, attention, and feeding behavior. Perhaps the most prominent noradrenergic neurons are sympathetic ganglion cells, which employ norepinephrine as the major peripheral transmitter in this division of the visceral motor system (see Chapter 20).

Norepinephrine synthesis requires dopamine β-hydroxylase, which catalyzes the production of norepinephrine from dopamine (see Figure 6.10). Norepinephrine is then loaded into synaptic vesicles via the same VMAT involved in vesicular dopamine transport. Norepinepherine is cleared from the synaptic cleft by the norepinepherine transporter (NET), which also is capable of taking up dopamine. As mentioned, NET serves as a molecular target of amphetamine, which acts as a stimulant by producing a net increase in the release of norepinepherine and dopamine. A mutation in the NET gene is a cause of orthostatic intolerance, a disorder that produces lightheadedness while standing up. Like dopamine, norepinepherine is degraded by MAO and COMT.

Norepinepherine, as well as epinephrine, acts on α- and β-adrenergic receptors (Figure 6.5B). Both types of receptor are G-protein-coupled; in fact, the β-adrenergic receptor was the first identified metabotropic neurotransmitter receptor. Two subclasses of α-adrenergic receptors are now known. Activation of α_1 receptors usually results in a slow depolarization linked to the inhibition of K^+ channels, while activation of α_2 receptors produces a slow hyperpolarization due to the activation of a different type of K^+ channel. There are three subtypes of β-adrenergic receptor, two of which are expressed in many types of neurons. Agonists and antagonists of adrenergic receptors, such as the β blocker propanolol (Inderol®), are used clinically for a variety of conditions ranging from cardiac arrhythmias to migraine headaches. However, most of the actions of these drugs are on smooth muscle receptors, particularly in the cardiovascular and respiratory systems (see Chapter 20).

- *Epinephrine* (also called adrenaline) is found in the brain at lower levels than the other catecholamines and also is present in fewer brain neurons than other catecholamines. Epinephrine-containing neurons in the central nervous system are primarily in the lateral tegmental system and in the medulla and project to the hypothalamus and thalamus (Figure 6.11C). The function of these epinepherine-secreting neurons is not known.

The enzyme that synthesizes epinephrine, phenylethanolamine-*N*-methyltransferase (see Figure 6.10), is present only in epinephrine-secreting neurons. Otherwise, the metabolism of epinepherine is very similar to that of norepinepherine. Epinepherine is loaded into vesicles via the VMAT. No plasma membrane transporter specific for epinepherine has been identified, though the NET is capable of transporting epinepherine. As already noted, epinepherine acts on both α- and β-adrenergic receptors.

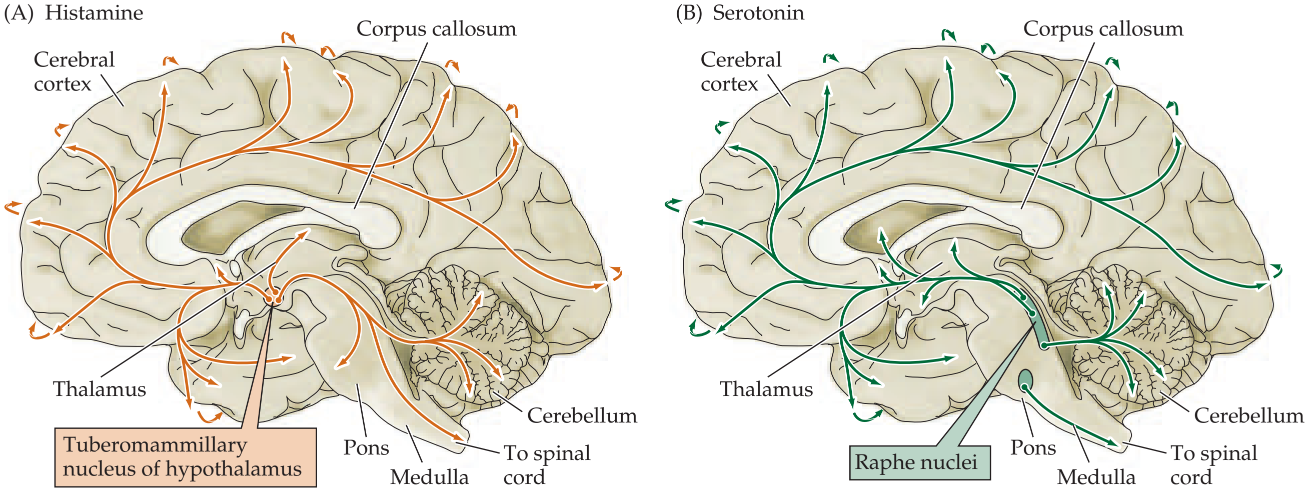


Figure 6.12 The distribution in the human brain of neurons and their projections (arrows) containing histamine (A) or serotonin (B). Curved arrows along the perimeter of the cortex indicate the innervation of lateral cortical regions not shown in this midsagittal plane of section.

sylvius

- *Histamine* is found in neurons in the hypothalamus that send sparse but widespread projections to almost all regions of the brain and spinal cord (Figure 6.12A). The central histamine projections mediate arousal and attention, similar to central ACh and norepinephrine projections. Histamine also controls the reactivity of the vestibular system. Allergic reactions or tissue damage cause release of histamine from mast cells in the bloodstream. The close proximity of mast cells to blood vessels, together with the potent actions of histamine on blood vessels, also raises the possibility that histamine may influence brain blood flow.

Histamine is produced from the amino acid histidine by a histidine decarboxylase (Figure 6.13A) and is transported into vesicles via the same VMAT as the catecholamines. No plasma membrane histamine transporter has been identified yet. Histamine is degraded by the combined actions of histamine methyltransferase and MAO.

There are three known types of histamine receptors, all of which are G-protein-coupled receptors (Figure 6.5B). Because of the importance of histamine receptors in the mediation of allergic responses, many histamine receptor antagonists have been developed as antihistamine agents. Antihistamines that cross the blood-brain barrier, such as diphenhydramine (Benadryl®), act as sedatives by interfering with the roles of histamine in CNS arousal. Antagonists of the H_1 receptor also are used to prevent motion sickness, perhaps because of the role of histamine in controling vestibular function. H_2 receptors control the secretion of gastric acid in the digestive system, allowing H_2 receptor antagonists to be used in the treatment of a variety of upper gastrointestinal disorders (e.g., peptic ulcers).

- *Serotonin*, or 5-hydroxytryptamine (5-HT), was initially thought to increase vascular tone by virtue of its presence in serum (hence the name serotonin). Serotonin is found primarily in groups of neurons in the raphe region of the pons and upper brainstem, which have widespread projections to the forebrain (see Figure 6.12B) and regulate sleep and wakefulness (see Chapter 27). 5-HT occupies a place of prominence in neuropharmacology because a large number of antipsychotic drugs that are valuable in the treatment of depression and anxiety act on serotonergic pathways (see Box E).

5-HT is synthesized from the amino acid tryptophan, which is an essential dietary requirement. Tryptophan is taken up into neurons by a plasma membrane transporter and hydroxylated in a reaction catalyzed by the enzyme tryptophan-5-hydroxylase (Figure 6.13B), the rate-limiting step for 5-HT synthesis. Loading of 5-HT into synaptic vesicles is done by the VMAT that is also responsible for loading of other monoamines into synaptic vesicles. The synaptic effects of serotonin are terminated by transport back into nerve terminals via a specific serotonin transporter (SERT). Many antidepressant drugs are selective serotonin reuptake inhibitors (SSRIs) that inhibit transport of 5-HT by SERT. Perhaps the best known example of an SSRI is Prozac (see Box E). The primary catabolic pathway for 5-HT is mediated by MAO.

A large number of 5-HT receptors have been identified. Most 5-HT receptors are metabotropic (see Figure 6.5B). These have been implicated in behaviors, including the emotions, circadian rhythms, motor behaviors, and state of mental arousal. Impairments in the function of these receptors have been implicated in numerous psychiatric disorders, such as depression, anxiety disorders, and schizophrenia (see Chapter 28), and drugs acting on serotonin receptors are effective treatments for a number of these conditions. Activation of 5-HT receptors also mediates satiety and decreased food consumption, which is why serotonergic drugs are sometimes useful in treating eating disorders.

Only one group of serotonin receptors, called the 5-HT_3 receptors, are ligand-gated ion channels (see Figure 6.4C). These are non-selective cation channels and therefore mediate excitatory postsynaptic responses. Their general structure, with functional channels formed by assembly of multiple subunits, is similar to the other ionotropic receptors described in the chapter. Two types of 5-HT_3 subunit are known, and form functional channels by assembling as a heteromultimer. 5-HT receptors are targets for a wide variety of therapeutic drugs including ondansetron (Zofran®) and granisetron (Kytril®), which are used to prevent postoperative nausea and chemotherapy-induced emesis.

ATP and Other Purines

Interestingly, all synaptic vesicles contain ATP, which is co-released with one or more "classical" neurotransmitters. This observation raises the possibility that ATP acts as a co-transmitter. It has been known since the 1920s that the extracellular application of ATP (or its breakdown products AMP and adenosine) can elicit electrical responses in neurons. The idea that some purines (so named because all these compounds contain a purine ring; see Figure 6.1) are also neurotransmitters has now received considerable experimental support. ATP acts as an excitatory neurotransmitter in motor neurons of the spinal cord, as well as sensory and autonomic ganglia. Postsynaptic actions of ATP have also been demonstrated in the central nervous system, specifically for dorsal horn neurons and in a subset of hippocampal neurons. Adenosine, however, cannot be considered a classical neurotransmitter because it is not stored in synaptic vesicles or released in a Ca^{2+}-dependent manner. Rather, it is generated from ATP by the action of extracellular enzymes. A number of enzymes, such as apyrase and ecto-5′ nucleotidase, as well as nucleoside transporters are involved in the rapid catabolism and removal of purines from extracellular locations. Despite the relative novelty of this evidence, it suggests that excitatory transmission via purinergic synapses is widespread in the mammalian brain.

In accord with this evidence, receptors for both ATP and adenosine are widely distributed in the nervous system, as well as many other tissues.

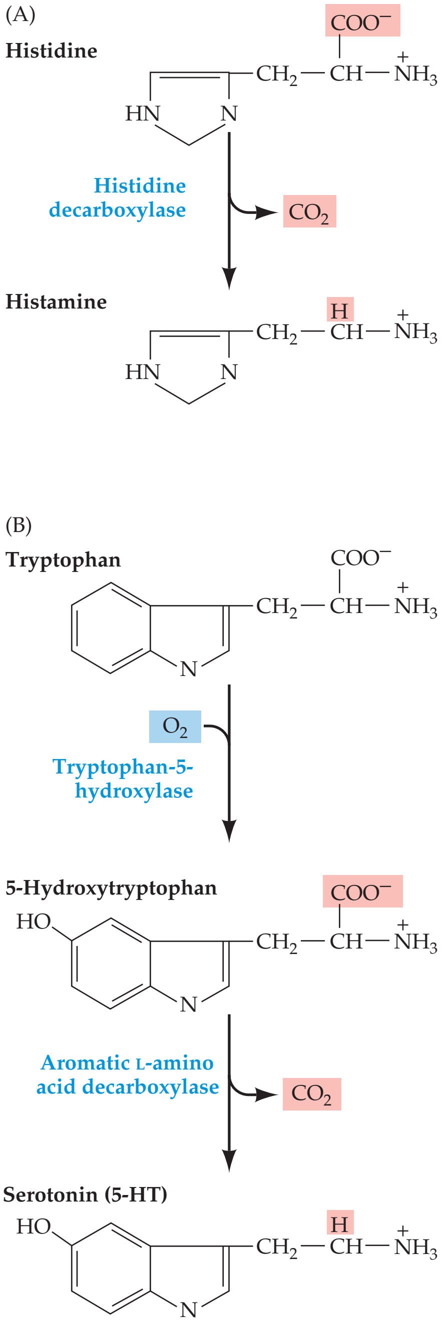


Figure 6.13 Synthesis of histamine and serotonin. (A) Histamine is synthesized from the amino acid histidine. (B) Serotonin is derived from the amino acid tryptophan by a two-step process that requires the enzymes tryptophan-5-hydroxylase and a decarboxylase.

Three classes of these purinergic receptors are now known. One of these classes consists of ligand-gated ion channels (see Figure 6.4C); the other two are G-protein-coupled metabotropic receptors (see Figure 6.5B). Like many ionotropic transmitter receptors, the ligand-gated channels are nonselective cation channels that mediate excitatory postsynaptic responses. The genes encoding these channels, however, are unique in that they appear to have only two transmembrane domains. Ionotropic purinergic receptors are widely distributed in central and peripheral neurons. In sensory nerves they evidently play a role in mechanosensation and pain; their function in most other cells, however, is not known.

The two types of metabotropic receptors activated by purines differ in their sensitivity to agonists: One type is preferentially stimulated by adenosine, whereas the other is preferentially activated by ATP. Both receptor types are found throughout the brain, as well as in peripheral tissues such as the heart, adipose tissue, and the kidney. Xanthines such as caffeine and theophylline block adenosine receptors, and this activity is thought to be responsible for the stimulant effects of these agents.

Peptide Neurotransmitters

Many peptides known to be hormones also act as neurotransmitters. Some peptide transmitters have been implicated in modulating emotions (see Chapter 28). Others, such as substance P and the opioid peptides, are involved in the perception of pain (see Chapter 9). Still other peptides, such as melanocyte-stimulating hormone, adrenocorticotropin, and β-endorphin, regulate complex responses to stress.

The mechanisms responsible for the synthesis and packaging of peptide transmitters are fundamentally different from those used for the small-molecule neurotransmitters and are much like the synthesis of proteins that are secreted from non-neuronal cells (pancreatic enzymes, for instance). Peptide-secreting neurons generally synthesize polypeptides in their cell bodies that are much larger than the final, “mature” peptide. Processing these polypeptides in their cell bodies, which are called **pre-propeptides** (or pre-proproteins), takes place by a sequence of reactions in several intracellular organelles. Pre-propeptides are synthesized in the rough endoplasmic reticulum, where the signal sequence of amino acids—that is, the sequence indicating that the peptide is to be secreted—is removed. The remaining polypeptide, called a **propeptide** (or proprotein), then traverses the Golgi apparatus and is packaged into vesicles in the *trans*-Golgi network. The final stages of peptide neurotransmitter processing occur after packaging into vesicles and involve proteolytic cleavage, modification of the ends of the peptide, glycosylation, phosphorylation, and disulfide bond formation.

Propeptide precursors are typically larger than their active peptide products and can give rise to more than one species of neuropeptide (Figure 6.14). The means that multiple neuroactive peptides can be released from a single vesicle. In addition, neuropeptides often are co-released with small-molecule neurotransmitters. Thus, peptidergic synapses often elicit complex postsynaptic responses. Peptides are catabolized into inactive amino acid fragments by enzymes called peptidases, usually located on the extracellular surface of the plasma membrane.

The biological activity of the peptide neurotransmitters depends on their amino acid sequence (Figure 6.15). Based on their amino acid sequences, neuropeptide transmitters have been loosely grouped into five categories:

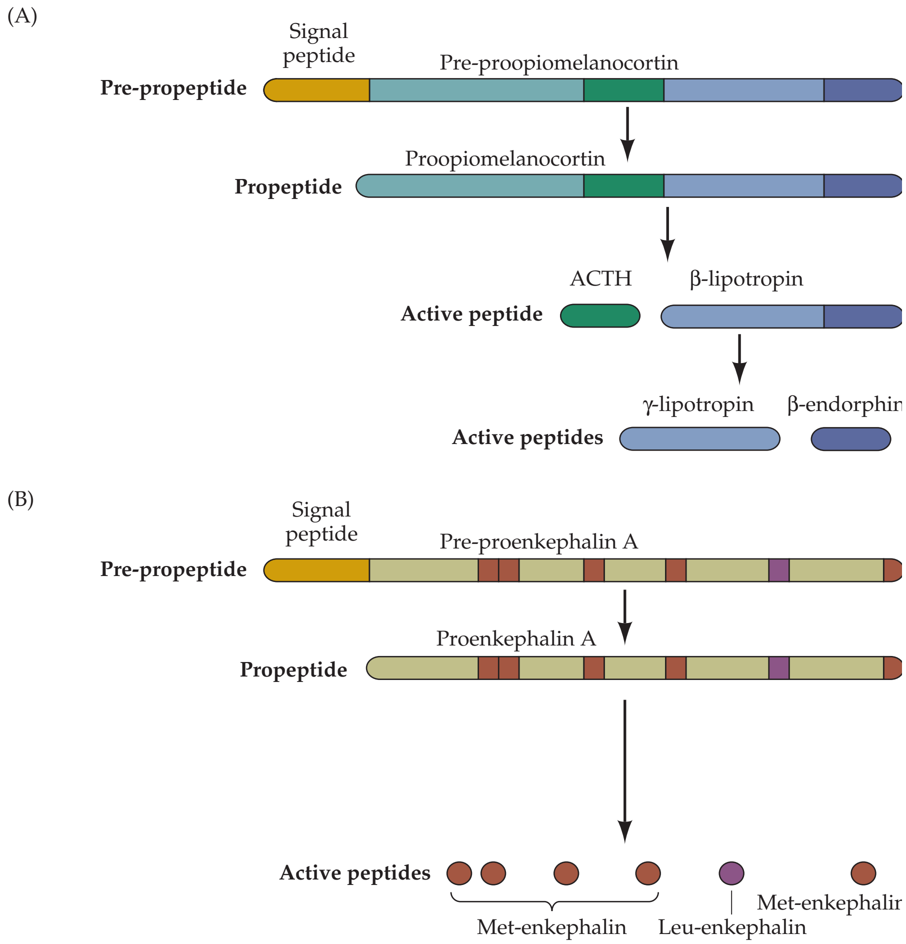

(A)
Signal peptide
Pre-proopiomelanocortin
Pre-propeptide
Proopiomelanocortin
Propeptide
ACTH
β-lipotropin
Active peptide
γ-lipotropin
β-endorphi
Active peptides
(B)
Signal peptide
Pre-proenkephalin A
Pre-propeptide
Proenkephalin A
Propeptide
Active peptides
Met-enkephalin
Leu-enkephalin
Met-enkephali

Figure 6.14 Proteolytic processing of the pre-propeptides pre-proopiomelanocortin (A) and pre-proenkephalin A (B). For each pre-propeptide, the signal sequence is indicated in orange at the left; the locations of active peptide products are indicated by different colors. The maturation of the pre-propeptides involves cleaving the signal sequence and other proteolytic processing. Such processing can result in a number of different neuroactive peptides such as ACTH, γ-lipotropin, and β-endorphin (A), or multiple copies of the same peptide, such as met-enkephalin (B).

the brain/gut peptides, opioid peptides, pituitary peptides, hypothalamic releasing hormones, and a catch-all category containing other peptides that are not easily classified.

Substance P is an example of the first of these categories (Figure 6.15A). The study of neuropeptides actually began more than 60 years ago with the accidental discovery of substance P, a powerful hypotensive agent. (The peculiar name derives from the fact that this molecule was an unidentified component of *powder* extracts from brain and intestine.) This 11-amino-acid peptide (see Figure 6.15) is present in high concentrations in the human hippocampus, neocortex, and also in the gastrointestinal tract; hence its classification as a brain/gut peptide. It is also released from C fibers, the small-diameter afferents in peripheral nerves that convey information about pain and temperature (as well as postganglionic autonomic signals). Substance P is a sensory neurotransmitter in the spinal cord, where its release can be inhibited by opioid peptides released from spinal cord interneurons, resulting in the suppression of pain (see Chapter 9). The diversity of neuropeptides is highlighted by the finding that the gene coding for substance P encodes a number of other neuroactive peptides including neurokinin A, neuropeptide K, and neuropeptide γ.

An especially important category of peptide neurotransmitters is the family of opioids (Figure 6.15B). These peptides are so named because they bind

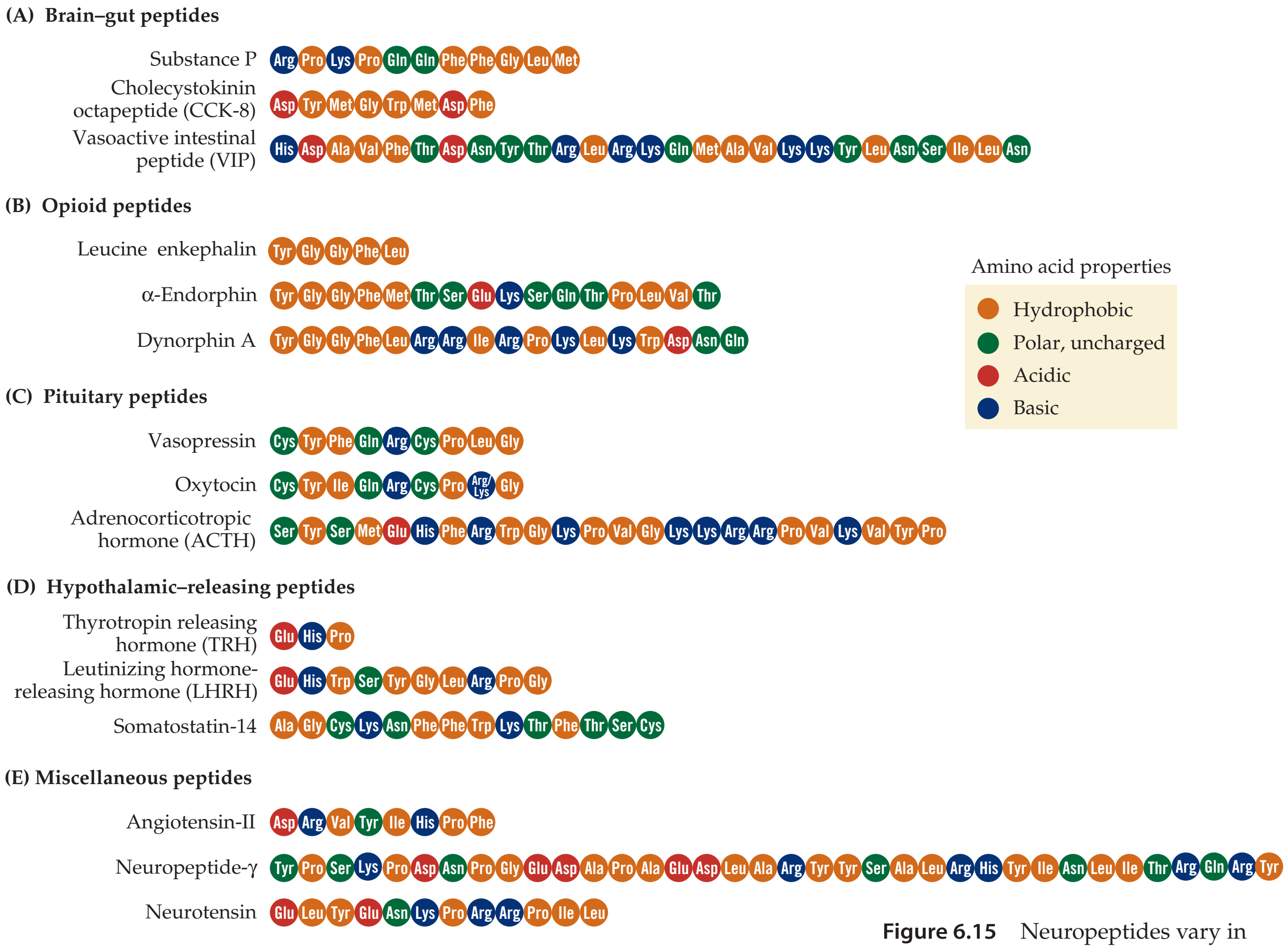

(A) Brain–gut peptides
Substance P
Arg Pro Lys Pro Gln Gln Phe Phe Gly Leu Met
Cholecystokinin octapeptide (CCK-8)
Asp Tyr Met Gly Trp Met Asp Phe
Vasoactive intestinal peptide (VIP)
His Asp Ala Val Phe Thr Asp Asn Tyr Thr Arg Leu Arg Lys Gln Met Ala Val Lys Lys Tyr Leu Asn Ser Ile Leu Asn
(B) Opioid peptides
Leucine enkephalin
Tyr Gly Gly Phe Leu
α-Endorphin
Tyr Gly Gly Phe Met Thr Ser Glu Lys Ser Gln Thr Pro Leu Val Thr
Dynorphin A
Tyr Gly Gly Phe Leu Arg Arg Ile Arg Pro Lys Leu Lys Trp Asp Asn Gln
(C) Pituitary peptides
Vasopressin
Cys Tyr Phe Gln Arg Cys Pro Leu Gly
Oxytocin
Cys Tyr Ile Gln Arg Cys Pro Arg/Lys Gly
Adrenocorticotropic hormone (ACTH)
Ser Tyr Ser Met Glu His Phe Arg Trp Gly Lys Pro Val Gly Lys Lys Arg Arg Pro Val Lys Val Tyr Pro
(D) Hypothalamic–releasing peptides
Thyrotropin releasing hormone (TRH)
Glu His Pro
Leutinizing hormone-releasing hormone (LHRH)
Glu His Trp Ser Tyr Gly Leu Arg Pro Gly
Somatostatin-14
Ala Gly Cys Lys Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys
(E) Miscellaneous peptides
Angiotensin-II
Asp Arg Val Tyr Ile His Pro Phe
Neuropeptide-γ
Tyr Pro Ser Lys Pro Asp Asn Pro Gly Glu Asp Ala Pro Ala Glu Asp Leu Ala Arg Tyr Tyr Ser Ala Leu Arg His Tyr Ile Asn Leu Ile Thr Arg Gln Arg Tyr
Neurotensin
Glu Leu Tyr Glu Asn Lys Pro Arg Arg Pro Ile Leu
Amino acid properties
● Hydrophobic
● Polar, uncharged
● Acidic
● Basic

Figure 6.15 Neuropeptides vary in length, but usually contain between 3 and 36 amino acids. The sequence of amino acids determines the biological activity of each peptide.

to the same postsynaptic receptors activated by opium. The opium poppy has been cultivated for at least 5000 years, and its derivatives have been used as an analgesic since at least the Renaissance. The active ingredients in opium are a variety of plant alkaloids, predominantly morphine. Morphine, named for Morpheus, the Greek god of dreams, is still one of the most effective analgesics in use today, despite its addictive potential (see Box A). Synthetic opiates such as meperidine and methadone are also used as analgesics, and fentanyl, a drug with 80 times the analgesic potency of morphine, is widely used in clinical anesthesiology.

The opioid peptides were discovered in the 1970s during a search for endorphins, *endo*genous compounds that mimicked the actions of m*orphin*e. It was hoped that such compounds would be analgesics, and that understanding them would shed light on drug addiction. The endogenous ligands of the opioid receptors have now been identified as a family of more than 20 opioid peptides that fall into three classes: the endorphins, the enkephalins, and the dynorphins (Table 6.2). Each of these classes are liberated from an inactive pre-propeptide (pre-proopiomelanocortin, pre-proenkephalin A, and pre-prodynorphin), derived from distinct genes (see Figure 6.14). Opioid precursor processing is carried out by tissue-specific processing enzymes that are packaged into vesicles, along with the precursor peptide, in the Golgi apparatus.

TABLE 6.2
Endogenous Opioid Peptides

Name	*Amino acid sequence*[a]
Endorphins	
α-Endorphin	*Tyr-Gly-Gly-Phe*-Met-Thr-Ser-Glu-Lys-Ser-Gln-Thr-Pro-Leu-Val-Thr
α-Neoendorphin	*Tyr-Gly-Gly-Phe*-Leu-Arg-Lys-Tyr-Pro-Lys
β-Endorphin	*Tyr-Gly-Gly-Phe*-Met-Thr-Ser-Glu-Lys-Ser-Gln-Thr-Pro-Leu-Val-Thr-Leu-Phe-Lys-Asn-Ala-Ile-Val-Lys-Asn-Ala-His-Lys-Gly-Gln
γ-Endorphin	*Tyr-Gly-Gly-Phe*-Met-Thr-Ser-Glu-Lys-Ser-Gln-Thr-Pro-Leu-Val-Thr-Leu
Enkephalins	
Leu-enkephalin	*Tyr-Gly-Gly-Phe*-Leu
Met-enkephalin	*Tyr-Gly-Gly-Phe*-Met
Dynorphins	
Dynorphin A	*Tyr-Gly-Gly-Phe*-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys-Trp-Asp-Asn-Gln
Dynorphin B	*Tyr-Gly-Gly-Phe*-Leu-Arg-Arg-Gln-Phe-Lys-Val-Val-Thr

[a] Note the initial homology, indicated by italics.

Opioid peptides are widely distributed throughout the brain and are often co-localized with other small-molecule neurotransmitters, such as GABA and 5-HT. In general, these peptides tend to be depressants. When injected intracerebrally in experimental animals, they act as analgesics; on the basis of this and other evidence, opioids are likely to be involved in the mechanisms underlying acupuncture-induced analgesia. Opioids are also involved in complex behaviors such as sexual attraction and aggressive/submissive behaviors. They have also been implicated in psychiatric disorders such as schizophrenia and autism, although the evidence for this is debated. Unfortunately, the repeated administration of opioids leads to tolerance and addiction.

Virtually all neuropeptides initiate their effects by activating G-protein-coupled receptors. The study of these metabotropic peptide receptors in the brain has been difficult because few specific agonists and antagonists are known. Peptides activate their receptors at low (nM to μM) concentrations compared to the concentrations required to activate receptors for small-molecule neurotransmitters. These properties allow the postsynaptic targets of peptides to be quite far removed from presynaptic terminals and to modulate the electrical properties of neurons that are simply in the vicinity of the site of peptide release. Neuropeptide receptor activation is especially important in regulating the postganglionic output from sympathetic ganglia and the activity of the gut (see Chapter 20). Peptide receptors, particularly the neuropeptide Y receptor, are also implicated in the initiation and maintenance of feeding behavior leading to satiety or obesity.

Other behaviors ascribed to peptide receptor activation include anxiety and panic attacks, and antagonists of cholecystokinin receptors are clinically useful in the treatment of these afflictions. Other useful drugs have been developed by targeting the opiate receptors. Three well-defined opioid receptor subtypes (μ, δ, and κ) play a role in reward mechanisms as well as addiction. The μ-opiate receptor has been specifically identified as the primary site for drug reward mediated by opiate drugs

Unconventional Neurotransmitters

In addition to the conventional neurotransmitters already described, some unusual molecules are also used for signaling between neurons and their targets. These chemical signals can be considered as neurotransmitters because of their roles in interneuronal signaling and because their release from neurons is regulated by Ca^{2+}. However, they are unconventional, in comparison to other neurotransmitters, because they are not stored in synaptic vesicles and are not released from presynaptic terminals via exocytotic mechanisms. In fact, these unconventional neurotransmitters need not be released from presynaptic terminals at all and are often associated with "retrograde" signaling from postsynaptic cells back to presynaptic terminals.

- *Endocannabinoids* are a family of related endogenous signals that interact with cannabinoid receptors. These receptors are the molecular targets of Δ^9-tetrahydrocannabinol, the psychoactive component of the marijuana plant, *Cannabis* (Box F). While some members of this emerging group of chemical signals remain to be determined, anandamide and 2-arachidonylglycerol (2-AG) have been established as endocannabinoids. These signals are unsaturated fatty acid with polar head groups and are produced by enzymatic degradation of membrane lipids (Figure 6.16A,B). Production of endocannabinoids is stimulated by a second messenger signal within postsynaptic neurons, typically a rise in postsynaptic Ca^{2+} concentration. Although the mechanism of endocannabinoid release is not entirely clear, it is likely that these hyrophobic signals diffuse through the postsynaptic membrane to reach cannabinoid receptors on other nearby cells. Endocannabinoid action is terminated by carrier-mediated transport of these signals back into the postsynaptic neuron. There they are hydrolyzed by the enzyme fatty acid hydrolase (FAAH).

At least two types of cannabinoid receptor have been identified, with most actions of endocannabinoids in the CNS mediated by the type termed CB1. CB1 is a G-protein-coupled receptor that is related to the metabotropic receptors for ACh, glutamate, and the other conventional neurotransmitters. Several compounds that are structurally related to endocannabinoids and that bind to the CB1 receptor have been synthesized (see Figure 6.16C). These compounds act as agonists or antagonists of the CB1 receptor and serve as both tools for elucidating the physiological functions of endocannabinoids and as targets for developing therapeutically useful drugs.

Endocannabinoids participate in several forms of synaptic regulation. The best-documented action of these agents is to inhibit communication between postsynaptic target cells and their presynaptic inputs. In both the hippocampus and the cerebellum, among other regions, endocannabinoids serve as retrograde signals to regulate GABA release at certain inhibitory terminals. At such synapses, depolarization of the postsynaptic neuron causes a transient reduction in inhibitory postsynaptic responses (Figure 6.17). Depolarization reduces synaptic transmission by elevating the concentration of Ca^{2+} within the postsynaptic neuron. This rise in Ca^{2+} triggers synthesis and release of endocannabinoids from the postsynaptic cells. The endocannabinoids then make their way to the presynaptic terminals and bind to CB1 receptors on these terminals. Activation of the CB1 receptors inhibits the amount of GABA released in response to presynaptic action potentials, thereby reducing inhibitory transmission. These mechanisms responsible for the reduction in GABA release are not entirely clear, but probably involve effects on voltage-gated Ca^{2+} channels and/or K^+ channels in the presynaptic neurons.

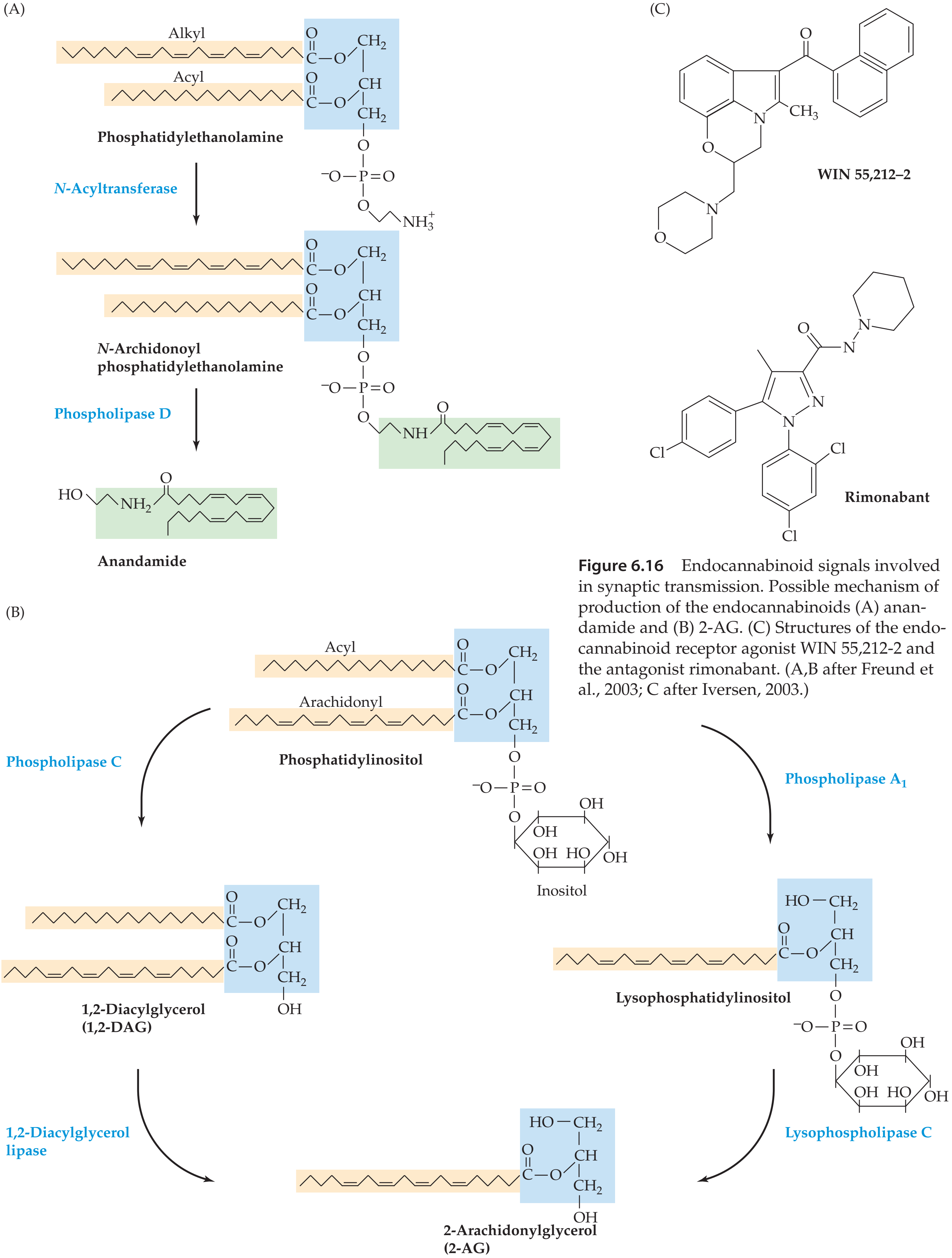

(A)
Alkyl
Acyl
Phosphatidylethanolamine
N-Acyltransferase
N-Archidonoyl phosphatidylethanolamine
Phospholipase D
Anandamide
(B)
Acyl
Arachidonyl
Phosphatidylinositol
Inositol
Phospholipase C
Phospholipase A1
1,2-Diacylglycerol (1,2-DAG)
Lysophosphatidylinositol
1,2-Diacylglycerol lipase
Lysophospholipase C
2-Arachidonylglycerol (2-AG)
(C)
WIN 55,212–2
Rimonabant

Figure 6.16 Endocannabinoid signals involved in synaptic transmission. Possible mechanism of production of the endocannabinoids (A) anandamide and (B) 2-AG. (C) Structures of the endocannabinoid receptor agonist WIN 55,212-2 and the antagonist rimonabant. (A,B after Freund et al., 2003; C after Iversen, 2003.)

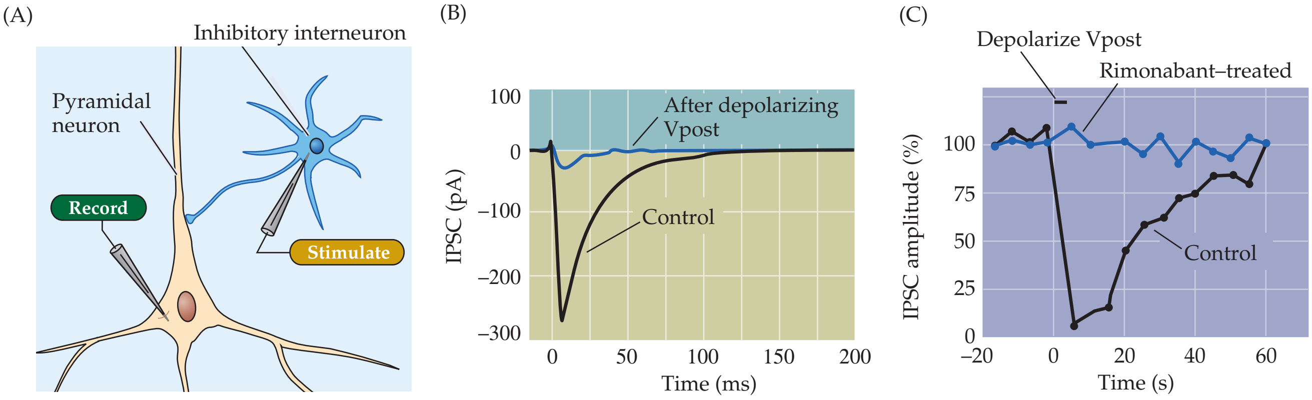
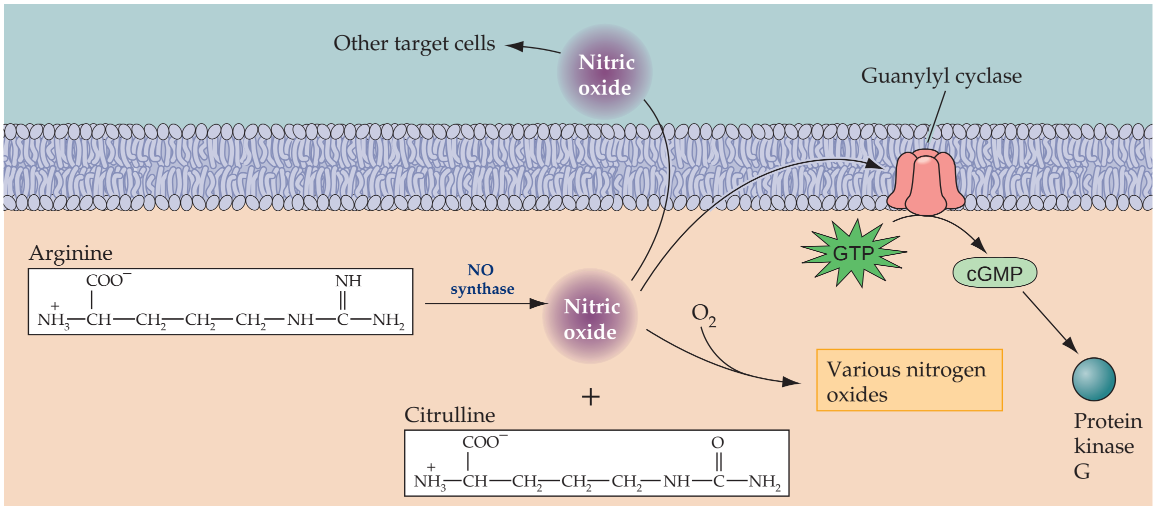


Figure 6.17 Endocannabinoid-mediated retrograde control of GABA release. (A) Experimental arrangement. Stimulation of a presynaptic interneuron causes release of GABA onto a postsynaptic pyramidal neuron. (B) IPSCs elicited by the inhibitory synapse (control) are reduced in amplitude following a brief depolarization of the postsynaptic neuron. This reduction in the IPSC is due to less GABA being released from the presynaptic interneuron. (C) The reduction in IPSC amplitude produced by postsynaptic depolarization lasts a few seconds and is mediated by endocannabinoids, because it is prevented by the endocannabinoid receptor antagonist rimonabant. (B,C after Ohno-Shosaku et al., 2001.)

•*Nitric oxide* (NO) is an unusual but especially interesting chemical signal. NO is a gas that is produced by the action of nitric oxide synthase, an enzyme that converts the amino acid arginine into a metabolite (citrulline) and simultaneously generates NO (Figure 6.18). NO is produced by an enzyme, nitric oxide synthase. Neuronal NO synthase is regulated by Ca^{2+} binding to the Ca^{2+} sensor protein calmodulin (see Chapter 7). Once produced, NO can permeate the plasma membrane, meaning that NO generated inside one cell can travel through the extracellular medium and act within nearby cells. Thus, this gaseous signal has a range of influence that extends well beyond the cell of origin, diffusing a few tens of micrometers from its site of production before it is degraded. This property makes NO a

Figure 6.18 Synthesis, release, and termination of NO.


Other target cells
Nitric oxide
Guanylyl cyclase
Arginine
COO⁻
NH
+NH3—CH—CH2—CH2—CH2—NH—C—NH2
NO synthase
Nitric oxide
O2
GTP
cGMP
Various nitrogen oxides
+
Citrulline
COO⁻
O
+NH3—CH—CH2—CH2—CH2—NH—C—NH2
Protein kinase G

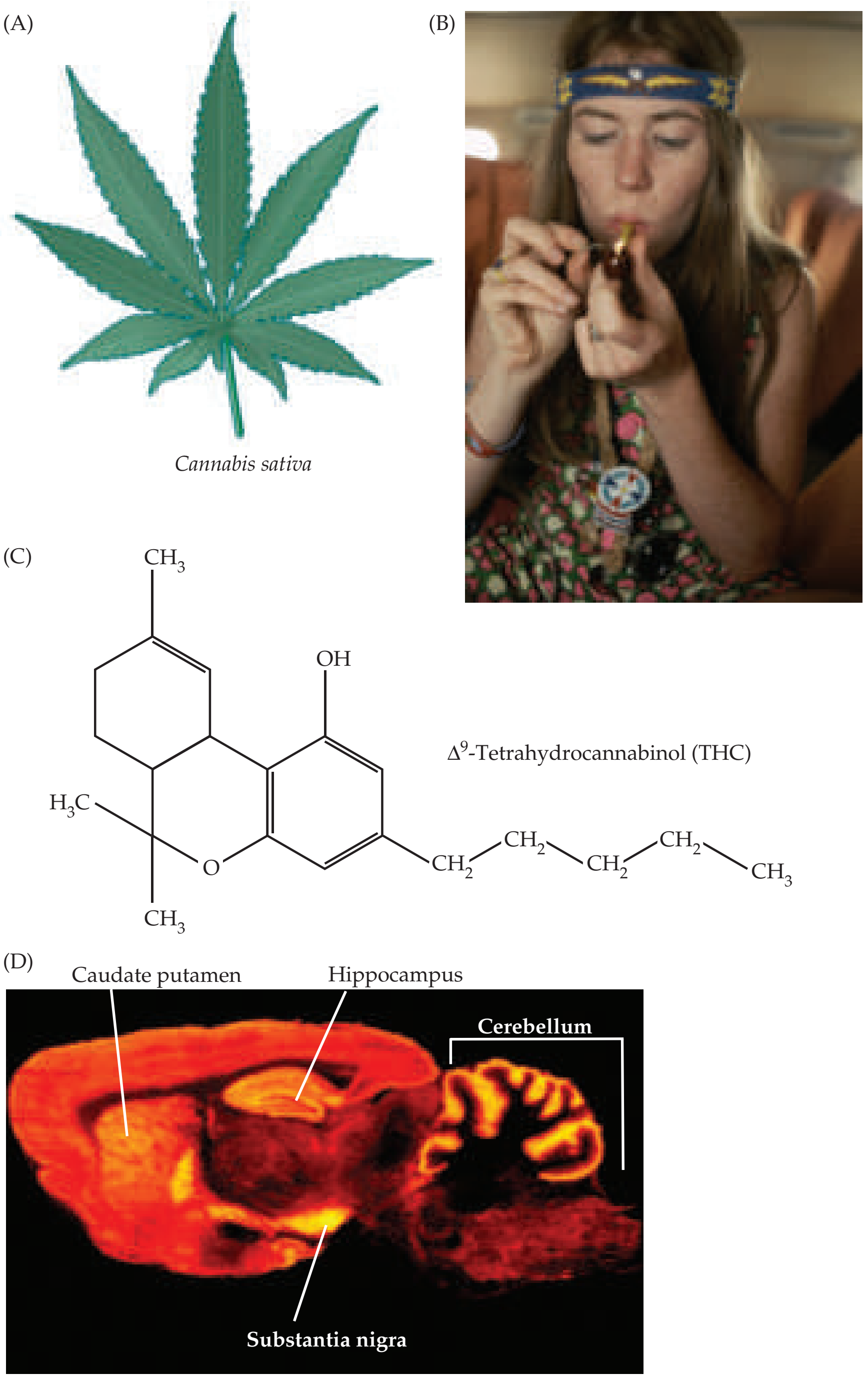
Box F

Marijuana and the Brain

Medicinal use of the marijuana plant, *Cannabis sativa* (Figure A), dates back thousands of years. Ancient civilizations—including both Greek and Roman societies in Europe, as well as Indian and Chinese cultures in Asia—appreciated that this plant was capable of producing relaxation, euphoria, and a number of other psychopharmacological actions. In more recent times, medicinal use of marijuana has largely subsided (although it remains useful in relieving the symptoms of terminal cancer patients); the recreational use of marijuana (Figure B) has become so popular that some societies have decriminalized its use.

Understanding the brain mechanisms underlying the actions of marijuana was advanced by the discovery that a cannabinoid, Δ^9-tetrahydrocannabinol (THC; Figure C), is the active component of marijuana. This finding led to the development of synthetic derivatives, such as WIN 55,212-2 and rimonabant (see Figure 6.16), that have served as valuable tools for probing the brain actions of THC. Of particular interest is that receptors for these cannabinoids exist in the brain and exhibit marked regional variations in distribution, being especially enriched in the brain areas—such as substantia nigra and caudate putamen—that have been implicated in drug abuse (Figure D). The presence of these brain receptors for cannabinoids led in turn to a search for endogenous cannabinoid compounds in the brain, culiminating in the discovery of endocannabinoids such as 2-AG and anandamide (see Figure 6.16). This path of discovery closely parallels the identification of endogenous opioid peptides, which resulted from the search for endogenous morphine-like compounds in the brain (see text and Table 6.2).

Given that THC interacts with brain endocannabinoid receptors, particularly



(A) Leaf of *Cannabis sativa*, the marijuana plant. (B) Smoking ground-up *Cannabis* leaves is a popular method of achieving the euphoric effects of marijuana. (C) Structure of THC (Δ^9-tetrahydrocannabinol), the active ingredient of marijuana. (D) Distribution of brain CB1 receptors, visualized by examining the binding of CP-55,940, a CB1 receptor ligand. (B photo © Henry Diltz/Corbis; C after Iversen, 2003; D courtesy of M. Herkenham, NIMH.)

the CB1 receptor, it is likely that such actions are responsible for the behavioral consequences of marijuana use. Indeed, many of the well-documented effects of marijuana are consistent with the distribution and actions of brain CB1 receptors. For example, marijuana effects on perception could be due to CB1 receptors in the neocortex, effects on psychomotor control due to endocannabinoid receptors in the basal ganglia and cerebellum, effects on short-term memory due to cannabinoid receptors in the hippocampus, and the well-known effects of marijuana on stimulating appetite due to hypothalamic actions. While formal links between these behavioral consequences of marijuana and the underlying brain mechanisms are still being forged, studies of the actions of this drug have shed substantial light on basic synaptic mechanisms, which promise to further elucidate the mode of action of one of the world's most popular drugs.

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potentially useful agent for coordinating the activities of multiple cells in a very localized region and may mediate certain forms of synaptic plasticity that spread within small networks of neurons.

All of the known actions of NO are mediated within its cellular targets; for this reason, NO often is considered a second messenger rather than a neurotransmitter. Some of these actions of NO are due to the activation of the enzyme guanylyl cyclase, which then produces the second messenger cGMP within target cells (see Chapter 7). Other actions of NO are the result of covalent modification of target proteins via nitrosylation, the addition of a nitryl group to selected amino acids within the proteins. NO decays spontaneously by reacting with oxygen to produce inactive nitrogen oxides. As a result, NO signals last for only a short time, on the order of seconds or less. NO signaling evidently regulates a variety of synapses that also employ conventional neurotransmitters; so far, presynaptic terminals that release glutamate are the best-studied target of NO in the central nervous system. NO may also be involved in some neurological diseases. For example, it has been proposed that an imbalance between nitric oxide and superoxide generation underlies some neurodegenerative diseases.

Summary

The complex synaptic computations occurring at neural circuits throughout the brain arise from the actions of a large number of neurotransmitters, which act on an even larger number of postsynaptic neurotransmitter receptors. Glutamate is the major excitatory neurotransmitter in the brain, whereas GABA and glycine are the major inhibitory neurotransmitters. The actions of these small-molecule neurotransmitters are typically faster than those of the neuropeptides. Thus, most small-molecule transmitters mediate synaptic transmission when a rapid response is essential, whereas the neuropeptide transmitters, as well as the biogenic amines and some small-molecule neurotransmitters, tend to modulate ongoing activity in the brain or in peripheral target tissues in a more gradual and ongoing way. Two broadly different families of neurotransmitter receptors have evolved to carry out the postsynaptic signaling actions of neurotransmitters. Ionotropic or ligand-gated ion channels combine the neurotransmitter receptor and ion channel in one molecular entity, and therefore give rise to rapid postsynaptic electrical responses. Metabotropic receptors regulate the activity of postsynaptic ion channels indirectly, usually via G-proteins, and induce slower and longer-lasting electrical responses. Metabotropic receptors are especially important in regulating behavior, and drugs targeting these receptors have been clinically valuable in treating a wide range of behavioral disorders. The postsynaptic response at a given synapse is determined by the combination of receptor subtypes, G-protein subtypes, and ion channels that are expressed in the postsynaptic cell. Because each of these features can vary both within and among neurons, a tremendous diversity of transmitter-mediated effects is possible. Drugs that influence transmitter actions have enormous importance in the treatment of neurological and psychiatric disorders, as well as in a broad spectrum of other medical problems.

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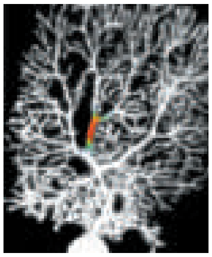
Chapter 7



Molecular Signaling within Neurons

Overview

As is apparent in the preceding chapters, electrical and chemical signaling mechanisms allow one nerve cell to receive and transmit information to another. This chapter focuses on the related events within neurons and other cells that are triggered by the interaction of a chemical signal with its receptor. This intracellular processing typically begins when extracellular chemical signals, such as neurotransmitters, hormones, and trophic factors, bind to specific receptors located either on the surface or within the cytoplasm or nucleus of the target cells. Such binding activates the receptors and in so doing stimulates cascades of intracellular reactions involving GTP-binding proteins, second messenger molecules, protein kinases, ion channels, and many other effector proteins whose modulation temporarily changes the physiological state of the target cell. These same intracellular signal transduction pathways can also cause longer-lasting changes by altering the transcription of genes, thus affecting the protein composition of the target cells on a more permanent basis. The large number of components involved in intracellular signaling pathways allows precise temporal and spatial control over the function of individual neurons, thereby allowing the coordination of electrical and chemical activity in the related populations of neurons that comprise neural circuits and systems.

Strategies of Molecular Signaling

Chemical communication coordinates the behavior of individual nerve and glial cells in physiological processes that range from neural differentiation to learning and memory. Indeed, molecular signaling ultimately mediates and modulates all brain functions. To carry out such communication, a series of extraordinarily diverse and complex chemical signaling pathways has evolved. The preceding chapters have described in some detail the electrical signaling mechanisms that allow neurons to generate action potentials for conduction of information. These chapters also described synaptic transmission, a special form of chemical signaling that transfers information from one neuron to another. Chemical signaling is not, however, limited to synapses (Figure 7.1A). Other well-characterized forms of chemical communication include **paracrine** signaling, which acts over a longer range than synaptic transmission and involves the secretion of chemical signals onto a group of nearby target cells, and **endocrine** signaling, which refers to the secretion of hormones into the bloodstream where they can affect targets throughout the body.

Chemical signaling of any sort requires three components: a molecular *signal* that transmits information from one cell to another, a *receptor* molecule

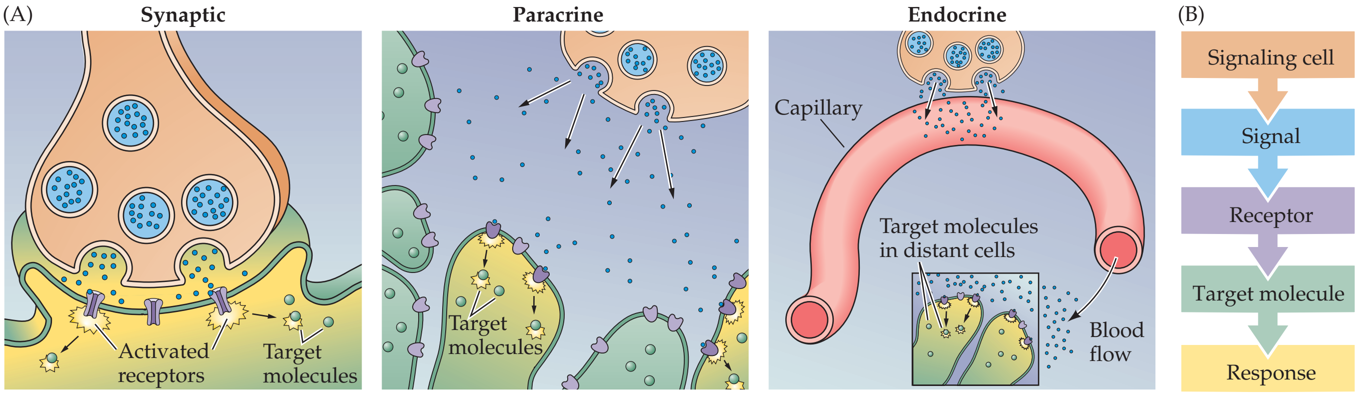


Figure 7.1 Chemical signaling mechanisms. (A) Forms of chemical communication include synaptic transmission, paracrine signaling, and endocrine signaling. (B) The essential components of chemical signaling are: cells that initiate the process by releasing signaling molecules; specific receptors on target cells; second messenger target molecules; and subsequent cellular responses.

that transduces the information provided by the signal, and a *target* molecule that mediates the cellular response (Figure 7.1B). The part of this process that take place within the confines of the target cell is called **intracellular signal transduction**. A good example of transduction in the context of *intercellular* communication is the sequence of events triggered by chemical synaptic transmission (see Chapter 5): Neurotransmitters serve as the signal, neurotransmitter receptors serve as the transducing receptor, and the target molecule is an ion channel that is altered to cause the electrical response of the postsynaptic cell. In many cases, however, synaptic transmission activates additional *intracellular* pathways that have a variety of functional consequences. For example, the binding of the neurotransmitter norepinephrine to its receptor activates GTP-binding proteins, which produces second messengers within the postsynaptic target, activates enzyme cascades, and eventually changes the chemical properties of numerous target molecules within the affected cell.

A general advantage of chemical signaling in both intercellular and intracellular contexts is **signal amplification**. Amplification occurs because individual signaling reactions can generate a much larger number of molecular products than the number of molecules that initiate the reaction. In the case of norepinephrine signaling, for example, a single norepinephrine molecule binding to its receptor can generate many thousands of second messenger molecules (such as cyclic AMP), yielding an amplification of tens of thousands of phosphates transferred to target proteins (Figure 7.2). Similar amplification occurs in all signal transduction pathways. Because the transduction processes often are mediated by a sequential set of enzymatic reactions, each with its own amplification factor, a small number of signal molecules ultimately can activate a very large number of target molecules. Such amplification guarantees that a physiological response is evoked in the face of other, potentially countervailing, influences.

Another rationale for these complex signal transduction schemes is to permit precise control of cell behavior over a wide range of times. Some molecular interactions allow information to be transferred rapidly, while others are slower and longer lasting. For example, the signaling cascades associated with synaptic transmission at neuromuscular junctions allow a person to respond to rapidly changing cues, such as the trajectory of a pitched ball, while the slower responses triggered by adrenal medullary hormones (epinephrine and norepinephrine) secreted during a challenging game produce slower (and longer lasting) effects on muscle metabolism (see Chapter 20) and emotional state (see Chapter 29). To encode information that varies so

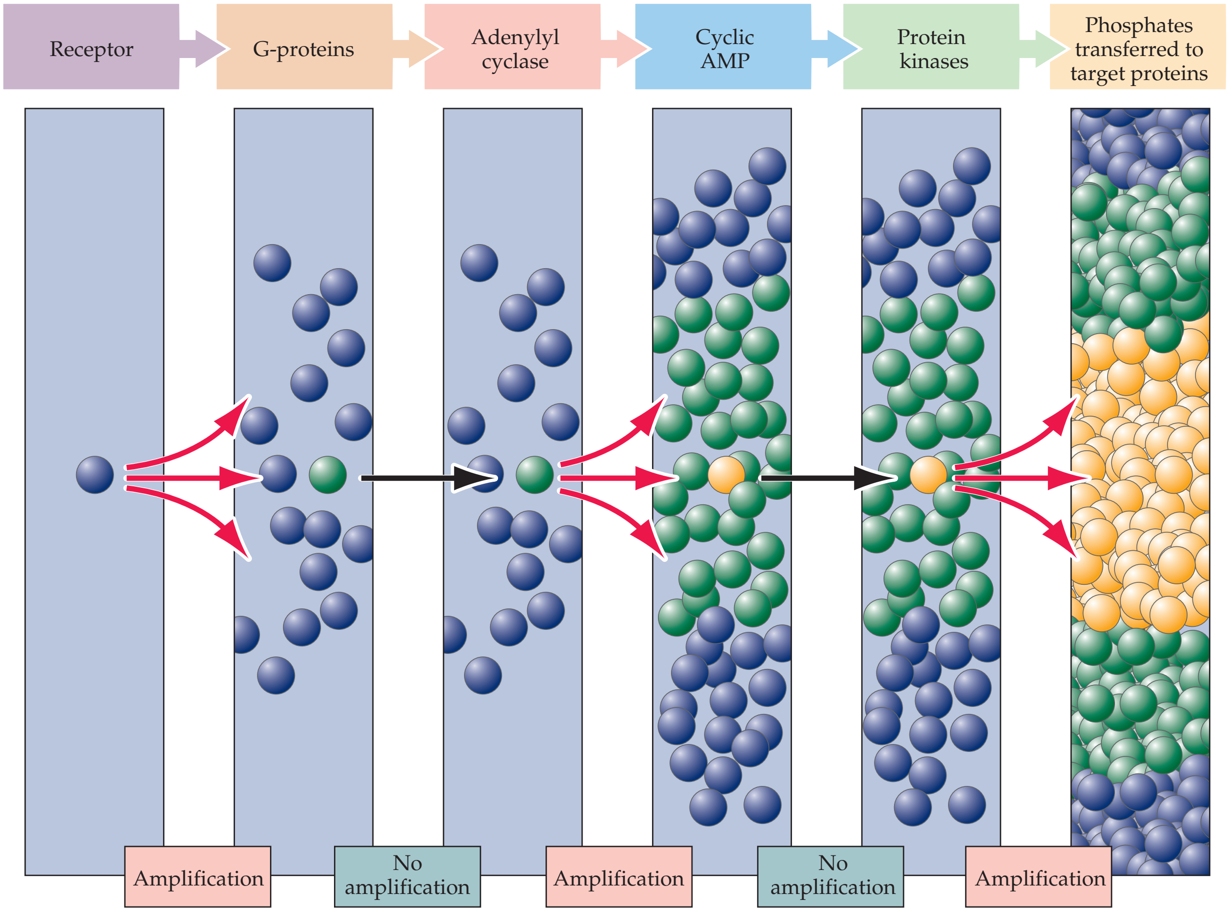


Figure 7.2 Amplification in signal transduction pathways. The activation of a single receptor by a signaling molecule, such as the neurotransmitter norepinephrine, can lead to the activation of numerous G-proteins inside cells. These activated proteins can bind to other signaling molecules, such as the enzyme adenylyl cyclase. Each activated enzyme molecule generates a large number of cAMP molecules. cAMP binds to and activates another family of enzymes, protein kinases. These enzymes can then phosphorylate many target proteins. While not every step in this signaling pathway involves amplification, overall the cascade results in a tremendous increase in the potency of the initial signal.

widely over time, the concentration of the relevant signaling molecules must be carefully controlled. On one hand, the concentration of every signaling molecule within the signaling cascade must return to subthreshold values before the arrival of another stimulus. On the other hand, keeping the intermediates in a signaling pathway activated is critical for a sustained response. Having multiple levels of molecular interactions facilitates the intricate timing of these events.

The Activation of Signaling Pathways

The molecular components of these signal transduction pathways are always activated by a chemical signaling molecule. Such signaling molecules can be grouped into three classes: **cell-impermeant**, **cell-permeant**, and **cell-associated signaling molecules** (Figure 7.3). The first two classes are secreted molecules and thus can act on target cells removed from the site of signal synthesis or release. Cell-impermeant signaling molecules typically bind to receptors associated with cell membranes. Hundreds of secreted molecules have now been identified, including the neurotransmitters discussed in Chapter 6, as well as proteins such as neurotrophic factors (see Chapter 22), and peptide hormones such as glucagon, insulin, and various reproductive hormones. These signaling molecules are typically short-lived, either because they are rapidly metabolized or because they are internalized by endocytosis once bound to their receptors.

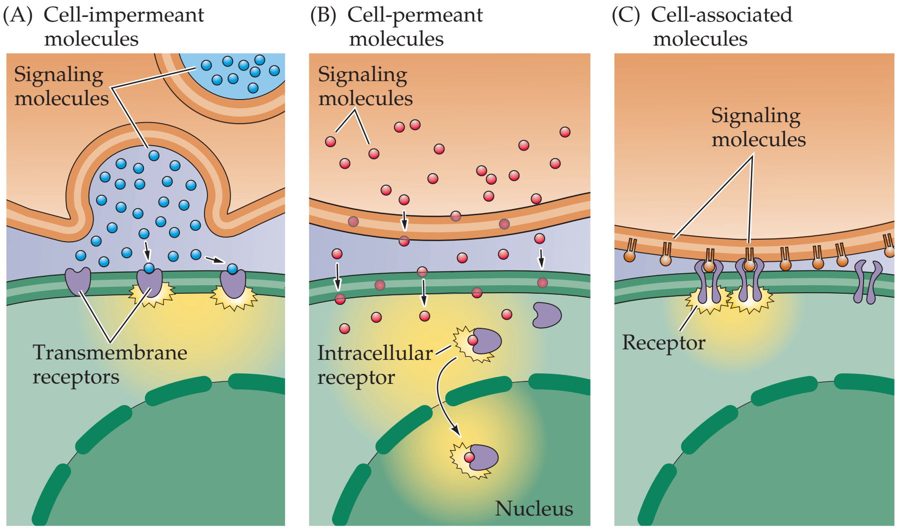


Figure 7.3 Three classes of cell signaling molecules. (A) Cell-impermeant molecules, such as neurotransmitters, cannot readily traverse the plasma membrane of the target cell and must bind to the extracellular portion of transmembrane receptor proteins. (B) Cell-permeant molecules are able to cross the plasma membrane and bind to receptors in the cytoplasm or nucleus of target cells. (C) Cell-associated molecules are presented on the extracellular surface of the plasma membrane. These signals activate receptors on target cells only if they are directly adjacent to the signaling cell.

Cell-permeant signaling molecules can cross the plasma membrane to act directly on receptors that are inside the cell. Examples include numerous steroid (glucocorticoids, estradiol, and testosterone) and thyroid (thyroxin) hormones, and retinoids. These signaling molecules are relatively insoluble in aqueous solutions and are often transported in blood and other extracellular fluids by binding to specific carrier proteins. In this form, they may persist in the bloodstream for hours or even days.

The third group of chemical signaling molecules, cell-associated signaling molecules, are arrayed on the extracellular surface of the plasma membrane. As a result, these molecules act only on other cells that are physically in contact with the cell that carries such signals. Examples include proteins such as the integrins and neural cell adhesion molecules (NCAMs) that influence axonal growth (see Chapter 22). Membrane-bound signaling molecules are more difficult to study, but are clearly important in neuronal development and other circumstances where physical contact between cells provides information about cellular identities.

Receptor Types

Regardless of the nature of the initiating signal, cellular responses are determined by the presence of receptors that specifically bind the signaling molecules. Binding of signal molecules causes a conformational change in the receptor, which then triggers the subsequent signaling cascade within the affected cell. Given that chemical signals can act either at the plasma membrane or within the cytoplasm (or nucleus) of the target cell, it is not surprising that receptors are actually found on both sides of the plasma membrane. The receptors for impermeant signal molecules are membrane-spanning proteins. The extracellular domain of such receptors includes the binding site for the signal, while the intracellular domain activates intracellular signaling cascades after the signal binds. A large number of these receptors have been identified and are grouped into families defined by the mechanism used to transduce signal binding into a cellular response (Figure 7.4).

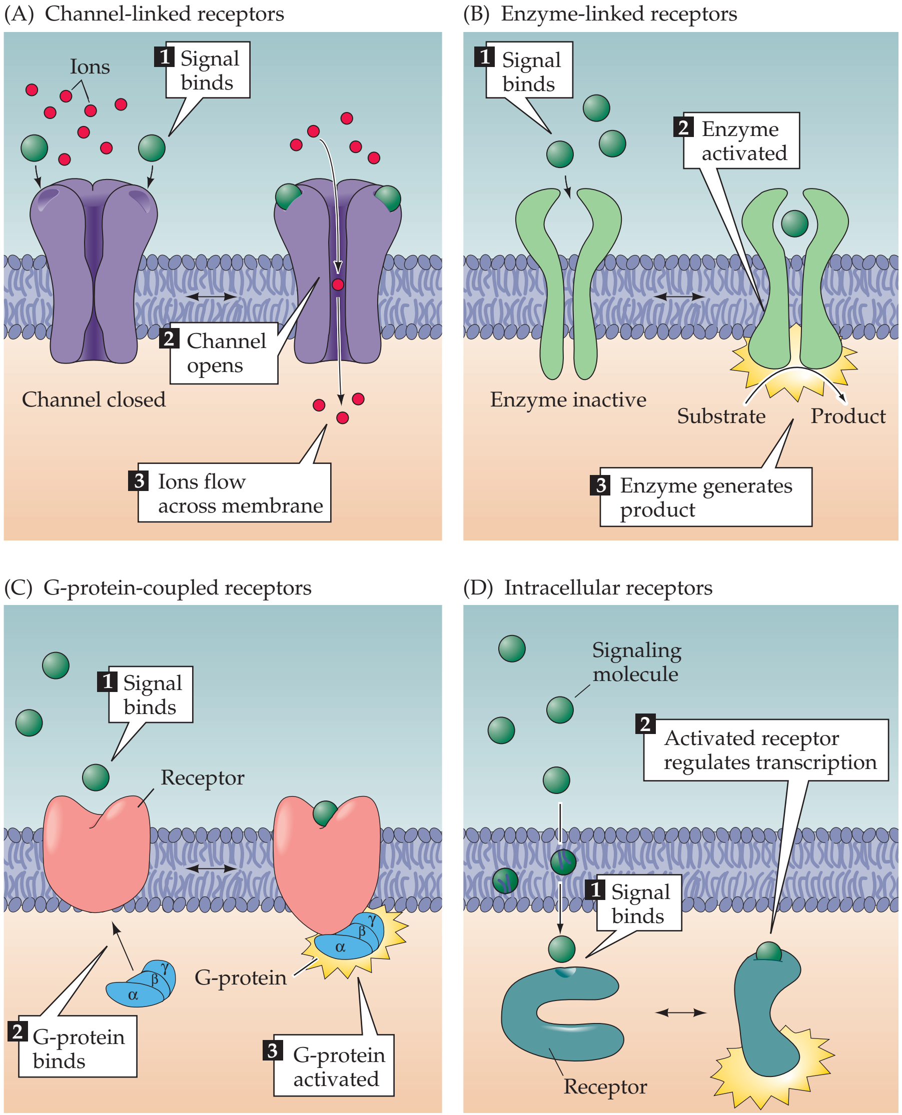

(A) Channel-linked receptors
Ions
1 Signal binds
2 Channel opens
Channel closed
3 Ions flow across membrane
(B) Enzyme-linked receptors
1 Signal binds
2 Enzyme activated
Enzyme inactive
Substrate
Product
3 Enzyme generates product
(C) G-protein-coupled receptors
1 Signal binds
Receptor
G-protein
α
β
γ
2 G-protein binds
3 G-protein activated
(D) Intracellular receptors
Signaling molecule
2 Activated receptor regulates transcription
1 Signal binds
Receptor

Figure 7.4 Categories of cellular receptors. Membrane-impermeant signaling molecules can bind to and activate either channel-linked receptors (A), enzyme-linked receptors (B), or G-protein-coupled receptors (C). Membrane permeant signaling molecules activate intracellular receptors (D).

Channel-linked receptors (also called ligand-gated ion channels) have the receptor and transducing functions as part of the same protein molecule. Interaction of the chemical signal with the binding site of the receptor causes the opening or closing of an ion channel pore in another part of the same molecule. The resulting ion flux changes the membrane potential of the target cell and, in some cases, can also lead to entry of Ca^{2+} ions that serve as a second messenger signal within the cell. Good examples of such receptors are the ionotropic neurotransmitter receptors described in Chapters 5 and 6.

Enzyme-linked receptors also have an extracellular binding site for chemical signals. The intracellular domain of such receptors is an enzyme whose catalytic activity is regulated by the binding of an extracellular signal. The great majority of these receptors are **protein kinases**, often tyrosine kinases, that phosphorylate intracellular target proteins, thereby changing the physiological function of the target cells. Noteworthy members of this group of receptors are the Trk family of neurotrophin receptors (see Chapter 22) and other receptors for growth factors.

G-protein-coupled receptors regulate intracellular reactions by an indirect mechanism involving an intermediate transducing molecule, called the **GTP-binding proteins** (or **G-proteins**). Because these receptors all share the structural feature of crossing the plasma membrane seven times, they are also referred to as 7-transmembrane receptors (or metabotropic receptors; see Chapter 5). Hundreds of different G-protein-linked receptors have been identified. Well-known examples include the β-adrenergic receptor, the muscarinic type of acetylcholine receptor, metabotropic glutamate receptors, receptors for odorants in the olfactory system, and many types of receptors for peptide hormones. Rhodopsin, a light-sensitive, 7-transmembrane protein in retinal photoreceptors, is another form of G-protein-linked receptor (see Chapter 10).

Intracellular receptors are activated by cell-permeant or lipophilic signaling molecules (Figure 7.4D). Many of these receptors lead to the activation of signaling cascades that produce new mRNA and protein within the target cell. Often such receptors comprise a receptor protein bound to an inhibitory protein complex. When the signaling molecule binds to the receptor, the inhibitory complex dissociates to expose a DNA-binding domain on the receptor. This activated form of the receptor can then move into the nucleus and directly interact with nuclear DNA, resulting in altered transcription. Some intracellular receptors are located primarily in the cytoplasm, while others are in the nucleus. In either case, once these receptors are activated they can affect gene expression by altering DNA transcription.

G-Proteins and Their Molecular Targets

Both G-protein-linked receptors and enzyme-linked receptors can activate biochemical reaction cascades that ultimately modify the function of target proteins. For both these receptor types, the coupling between receptor activation and their subsequent effects are the GTP-binding proteins. There are two general classes of GTP-binding protein (Figure 7.5). **Heterotrimeric G-proteins** are composed of three distinct subunits (α, β, and γ). There are many different α, β, and γ subunits, allowing a bewildering number of G-protein permutations. Regardless of the specific composition of the heterotrimeric G-protein, its α subunit binds to guanine nucleotides, either GTP or GDP. Binding of GDP then allows the α subunit to bind to the β and γ subunits to form an inactive trimer. Binding of an extracellular signal to a G-protein-coupled receptor in turn allows the G-protein to bind to the receptor and causes GDP to be replaced with GTP (Figure 7.5A). When GTP is bound to the G-protein, the α subunit dissociates from the βγ complex and activates the G-protein. Following activation, both the GTP-bound α subunit and the free βγ complex can bind to downstream effector molecules that mediate a variety of responses in the target cell.

The second class of GTP-binding proteins are **monomeric G-proteins** (also called **small G-proteins**). These monomeric GTPases also relay signals from activated cell surface receptors to intracellular targets such as the cytoskeleton and the vesicle trafficking apparatus of the cell. The first small G-protein was discovered in a virus that causes *ra*t *s*arcoma tumors and was therefore called **ras**. Ras is a molecule that helps regulate cell differentiation and proliferation by relaying signals from receptor kinases to the nucleus; the viral form of ras is defective, which accounts for the ability of the virus to cause the uncontrolled cell proliferation that leads to tumors. Since then, a

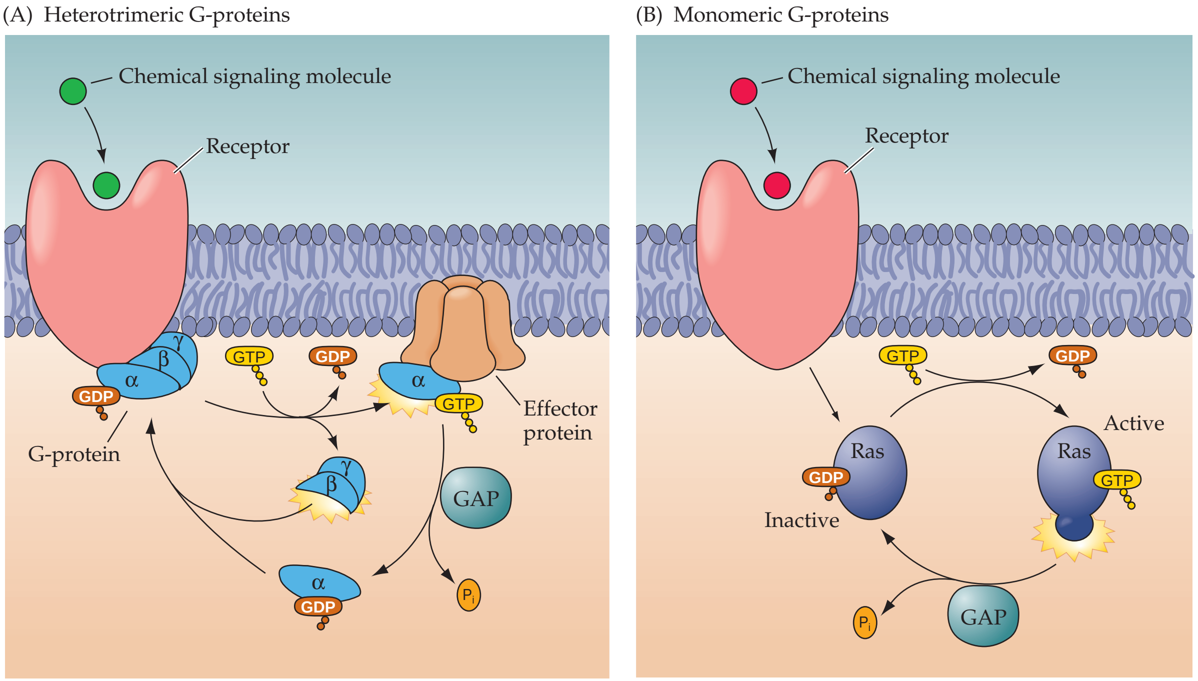


Figure 7.5 Types of GTP-binding protein. (A) Heterotrimeric G-proteins are composed of three distinct subunits (α, β, and γ). Receptor activation causes the binding of the G-protein and the α subunit to exchange GDP for GTP, leading to a dissociation of the α and βγ subunits. The biological actions of these G-proteins are terminated by hydrolysis of GTP, which is enhanced by GTPase-activating (GAP) proteins. (B) Monomeric G-proteins use similar mechanisms to relay signals from activated cell surface receptors to intracellular targets. Binding of GTP stimulates the biological actions of these G-proteins, and their activity is terminated by hydrolysis of GTP, which is also regulated by GAP proteins.

large number of small GTPases have been identified and can be sorted into five different subfamilies with different functions. For instance, some are involved in vesicle trafficking in the presynaptic terminal or elsewhere in the neuron, while others play a central role in protein and RNA trafficking in and out of the nucleus.

Termination of signaling by both heterotrimeric and monomeric G-proteins is determined by hydrolysis of GTP to GDP. The rate of GTP hydrolysis is an important property of a particular G-protein that can be regulated by other proteins, termed GTPase-activating proteins (GAPs). By replacing GTP with GDP, GAPs return G-proteins to their inactive form. GAPs were first recognized as regulators of small G-proteins, but recently similar proteins have been found to regulate the α subunits of heterotrimeric G-proteins. Hence, monomeric and trimeric G-proteins function as molecular timers that are active in their GTP-bound state, and become inactive when they have hydrolized the bound GTP to GDP (Figure 7.5B).

Activated G-proteins alter the function of many downstream effectors. Most of these effectors are enzymes that produce intracellular second messengers. Effector enzymes include adenylyl cyclase, guanylyl cyclase, phospholipase C, and others (Figure 7.6). The second messengers produced by these enzymes trigger the complex biochemical signaling cascades discussed in the next section. Because each of these cascades is activated by specific G-protein subunits, the pathways activated by a particular receptor are determined by the specific identity of the G-protein subunits associated with it.

As well as activating effector molecules, G-proteins can also directly bind to and activate ion channels. For example, some neurons, as well as heart muscle cells, have G-protein-coupled receptors that bind acetylcholine. Because these receptors are also activated by the agonist muscarine, they are usually called muscarinic receptors (see Chapters 6 and 20). Activation of muscarinic receptors can open K^+ channels, thereby inhibiting the rate at which the neuron fires action potentials, or slowing the heartbeat of muscle

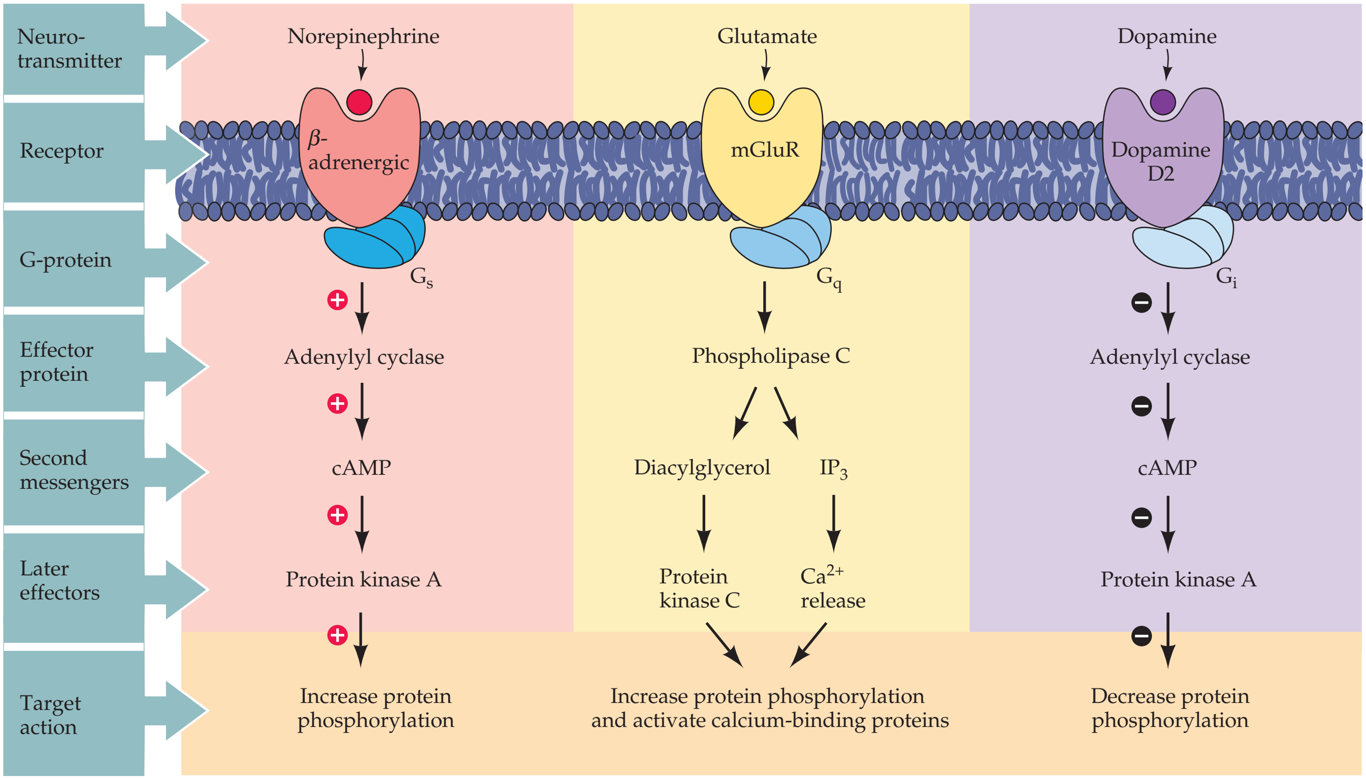

Neuro-transmitter
Receptor
G-protein
Effector protein
Second messengers
Later effectors
Target action
Norepinephrine
β-adrenergic
G_s
Adenylyl cyclase
cAMP
Protein kinase A
Increase protein phosphorylation
Glutamate
mGluR
G_q
Phospholipase C
Diacylglycerol
IP_3
Protein kinase C
Ca^{2+} release
Increase protein phosphorylation and activate calcium-binding proteins
Dopamine
Dopamine D2
G_i
Adenylyl cyclase
cAMP
Protein kinase A
Decrease protein phosphorylation

Figure 7.6 Effector pathways associated with G-protein-coupled receptors. In all three examples shown here, binding of a neurotransmitter to such a receptor leads to activation of a G-protein and subsequent recruitment of second messenger pathways. G_s, G_q, and G_i refer to three different types of heterotrimeric G-protein.

cells. These inhibitory responses are believed to be the result of βγ subunits of G-proteins binding to the K^+ channels. The activation of α subunits can also lead to the rapid closing of voltage-gated Ca^{2+} and Na^+ channels. Because these channels carry inward currents involved in generating action potentials, closing them makes it more difficult for target cells to fire (see Chapters 3 and 4).

In summary, the binding of chemical signals to their receptors activates cascades of signal transduction events in the cytosol of target cells. Within such cascades, G-proteins serve a pivotal function as the molecular transducing elements that couple membrane receptors to their molecular effectors within the cell. The diversity of G-proteins and their downstream targets leads to many types of physiological responses. By directly regulating the gating of ion channels, G-proteins can influence the membrane potential of target cells.

Second Messengers

Neurons use many different second messengers as intracellular signals. These messengers differ in the mechanism by which they are produced and removed, as well as their downstream targets and effects (Figure 7.7A). This section summarizes the attributes of some of the principal second messengers.

- *Calcium.* The calcium ion (Ca^{2+}) is perhaps the most common intracellular messenger in neurons. Indeed, few neuronal functions are immune to the influence—direct or indirect—of Ca^{2+}. In all cases, information is transmitted by a transient rise in the cytoplasmic calcium concentration, which

(A)

Second messenger	**Sources**	**Intracellular targets**	**Removal mechanisms**
Ca^{2+}	Plasma membrane: Voltage-gated Ca^{2+} channels Various ligand-gated channels Endoplasmic reticulum: IP_3 receptors Ryanodine receptors	Calmodulin Protein kinases Protein phosphatases Ion channels Synaptotagmin Many other Ca^{2+}-binding proteins	Plasma membrane: Na^+/Ca^{2+} exchanger Ca^{2+} pump Endoplasmic reticulum: Ca^{2+} pump Mitochondria
Cyclic AMP	Adenylyl cyclase acts on ATP	Protein kinase A Cyclic nucleotide-gated channels	cAMP phosphodiesterase
Cyclic GMP	Guanylyl cyclase acts on GTP	Protein kinase G Cyclic nucleotide-gated channels	cGMP phosphodiesterase
IP_3	Phospholipase C acts on PIP_2	IP_3 receptors on endoplasmic reticulum	Phosphatases
Diacylglycerol	Phospholipase C acts on PIP_2	Protein kinase C	Various enzymes

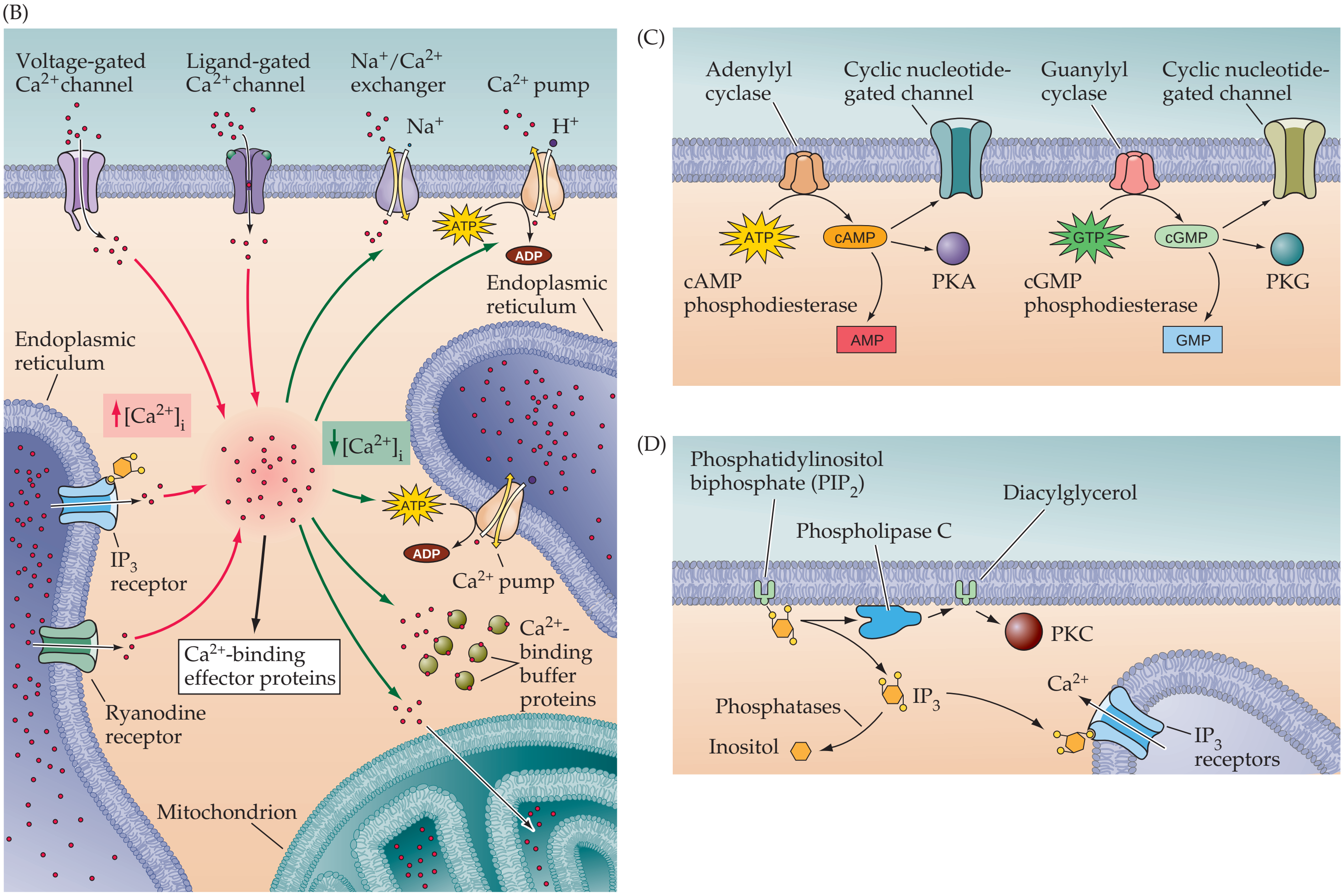

(B)
Voltage-gated Ca^{2+} channel
Ligand-gated Ca^{2+} channel
Na^+/Ca^{2+} exchanger
Ca^{2+} pump
Na^+
H^+
ATP
ADP
Endoplasmic reticulum
Endoplasmic reticulum
↑$[Ca^{2+}]_i$
↓$[Ca^{2+}]_i$
ATP
ADP
IP_3 receptor
Ca^{2+} pump
Ca^{2+}-binding effector proteins
Ca^{2+}-binding buffer proteins
Ryanodine receptor
Mitochondrion
(C)
Adenylyl cyclase
Cyclic nucleotide-gated channel
Guanylyl cyclase
Cyclic nucleotide-gated channel
ATP
cAMP
GTP
cGMP
cAMP phosphodiesterase
PKA
cGMP phosphodiesterase
PKG
AMP
GMP
(D)
Phosphatidylinositol biphosphate (PIP_2)
Diacylglycerol
Phospholipase C
PKC
Ca^{2+}
IP_3
Phosphatases
Inositol
IP_3 receptors

Figure 7.7 Neuronal second messengers. (A) Mechanisms responsible for producing and removing second messengers, as well as the downstream targets of these messengers. (B) Proteins involved in delivering calcium to the cytoplasm and in removing calcium from the cytoplasm. (C) Mechanisms of production and degradation of cyclic nucleotides. (D) Pathways involved in production and removal of diacylglycerol (DAG) and IP_3.

allows Ca^{2+} to bind to a large number of Ca^{2+}-binding proteins that serve as molecular targets. One of the most thoroughly studied targets of Ca^{2+} is **calmodulin**, a Ca^{2+}-binding protein abundant in the cytosol of all cells. Binding of Ca^{2+} to calmodulin activates this protein, which then initiates its effects by binding to still other downstream targets, such as protein kinases.

Ordinarily the concentration of Ca^{2+} ions in the cytosol is extremely low, typically 50–100 nanomolar (10^{-9} *M*). The concentration of Ca^{2+} ions outside neurons—in the bloodstream or cerebrospinal fluid, for instance—is several orders of magnitude higher, typically several millimolar (10^{-3} *M*). This steep Ca^{2+} gradient is maintained by a number of mechanisms (Figure 7.7B). Most important in this maintenance are two proteins that translocate Ca^{2+} from the cytosol to the extracellular medium: an ATPase called the **calcium pump**, and an **Na^+/Ca^{2+} exchanger**, which is a protein that replaces intracellular Ca^{2+} with extracellular sodium ions (see Chapter 4). In addition to these plasma membrane mechanisms, Ca^{2+} is also pumped into the endoplasmic reticulum and mitochondria. These organelles can thus serve as storage depots of Ca^{2+} ions that are later released to participate in signaling events. Finally, nerve cells contain other Ca^{2+}-binding proteins—such as **calbindin**—that serve as Ca^{2+} buffers. Such buffers reversibly bind Ca^{2+} and thus blunt the magnitude and kinetics of Ca^{2+} signals within neurons.

The Ca^{2+} ions that act as intracellular signals enter cytosol by means of one or more types of Ca^{2+}-permeable ion channels (see Chapter 4). These can be voltage-gated Ca^{2+} channels or ligand-gated channels in the plasma membrane, both of which allow Ca^{2+} to flow down the Ca^{2+} gradient and into the cell from the extracellular medium. In addition, other channels allow Ca^{2+} to be released from the interior of the endoplasmic reticulum into the cytosol. These intracellular Ca^{2+}-releasing channels are gated, so they can be opened or closed in response to various intracellular signals. One such channel is the **inositol trisphosphate (IP_3) receptor.** As the name implies, these channels are regulated by IP_3, a second messenger described in more detail below. A second type of intracellular Ca^{2+}-releasing channel is the **ryanodine receptor,** named after a drug that binds to and partially opens these receptors. Among the biological signals that activate ryanodine receptors are cytoplasmic Ca^{2+} and, at least in muscle cells, depolarization of the plasma membrane.

These various mechanisms for elevating and removing Ca^{2+} ions allow precise control of both the timing and location of Ca^{2+} signaling within neurons, which in turn permit Ca^{2+} to control many different signaling events. For example, voltage-gated Ca^{2+} channels allow Ca^{2+} concentrations to rise very rapidly and locally within presynaptic terminals to trigger neurotransmitter release, as already described in Chapter 5. Slower and more widespread rises in Ca^{2+} concentration regulate a wide variety of other responses, including gene expression in the cell nucleus.

- *Cyclic nucleotides.* Another important group of second messengers are the cyclic nucleotides, specifically cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) (Figure 7.7C). Cyclic AMP is a derivative of the common cellular energy storage molecule, ATP. Cyclic AMP is produced when G-proteins activate adenylyl cyclase in the plasma membrane. This enzyme converts ATP into cAMP by removing two phosphate groups from the ATP. Cyclic GMP is similarly produced from GTP by the action of guanylyl cyclase. Once the intracellular concentration of cAMP or cGMP is elevated, these nucleotides can bind to two different classes of targets. The most common targets of cyclic nucleotide action are protein kinases, either the cAMP-dependent protein kinase (PKA) or the cGMP-dependent protein kinase (PKG). These enzymes mediate many physiological responses by phosphorylating target proteins, as described in the following section. In addition, cAMP and cGMP can bind to certain ligand-gated ion channels, thereby influencing neuronal signaling. These cyclic nucleotide-gated channels are particularly important in phototransduction and other sensory transduction processes, such as olfaction. Cyclic nucleotide signals are degraded by phosphodiesterases, enzymes that cleave phosphodiester bonds and convert cAMP into AMP or cGMP into GMP.

- *Diacylglycerol and IP$_3$*. Remarkably, membrane lipids can also be converted into intracellular second messengers (Figure 7.7D). The two most important messengers of this type are produced from phosphatidylinositol bisphosphate (PIP$_2$). This lipid component is cleaved by phospholipase C, an enzyme activated by certain G-proteins and by calcium ions. Phospholipase C splits the PIP$_2$ into two smaller molecules that each act as second messengers. One of these messengers is diacylglycerol (DAG), a molecule that remains within the membrane and activates protein kinase C, which phosphorylates substrate proteins in both the plasma membrane and elsewhere. The other messenger is inositol trisphosphate (IP$_3$), a molecule that leaves the cell membrane and diffuses within the cytosol. IP$_3$ binds to IP$_3$ receptors, channels that release calcium from the endoplasmic reticulum. Thus, the action of IP$_3$ is to produce yet another second messenger (perhaps a third messenger, in this case!) that triggers a whole spectrum of reactions in the cytosol. The actions of DAG and IP$_3$ are terminated by enzymes that convert these two molecules into inert forms that can be recycled to produce new molecules of PIP$_2$.

Second Messenger Targets: Protein Kinases and Phosphatases

As already mentioned, second messengers typically regulate neuronal functions by modulating the phosphorylation state of intracellular proteins (Figure 7.8). Phosphorylation (the addition of phosphate groups) rapidly and reversibly changes protein function. Proteins are phosphorylated by a wide variety of **protein kinases**; phosphate groups are removed by other enzymes called **protein phosphatases**. The degree of phosphorylation of a target protein thus reflects a balance between the competing actions of protein kinases and phosphatases, thus integrating a host of cellular signaling pathways. The substrates of protein kinases and phosphatases include enzymes, neurotransmitter receptors, ion channels, and structural proteins.

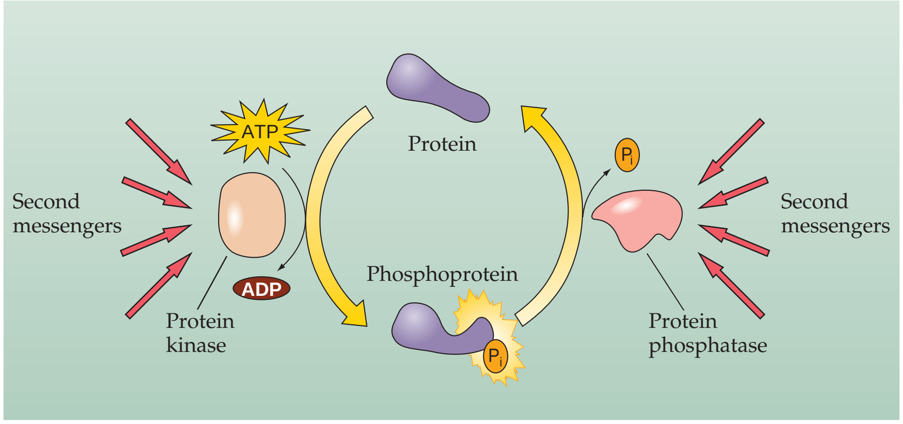


Figure 7.8 Regulation of cellular proteins by phosphorylation. Protein kinases transfer phosphate groups (P$_i$) from ATP to serine, threonine, or tyrosine residues on substrate proteins. This phosphorylation reversibly alters the structure and function of cellular proteins. Removal of the phosphate groups is catalyzed by protein phosphatases. Both kinases and phosphatases are regulated by a variety of intracellular second messengers.

Protein kinases and phosphatases typically act either on the serine and threonine residues (Ser/Thr kinases or phosphatases) or the tyrosine residues (Tyr kinases or phosphatases) of their substrates. Some of these enzymes act specifically on only one or a handful of protein targets, while others are multifunctional and have a broad range of substrate proteins. The activity of protein kinases and phosphatases can be regulated either by second messengers, such as cAMP or Ca^{2+}, or by extracellular chemical signals, such as growth factors (see Chapter 22). Typically, second messengers activate Ser/Thr kinases, whereas extracellular signals activate Tyr kinases. Although thousands of protein kinases are expressed in the brain, a relatively small number function as regulators of neuronal signaling.

- *cAMP-dependent protein kinase (PKA).* The primary effector of cAMP is the cAMP-dependent protein kinase (PKA). PKA is a tetrameric complex of two catalytic subunits and two inhibitory (regulatory) subunits. cAMP activates PKA by binding to the regulatory subunits and causing them to release active catalytic subunits. Such displacement of inhibitory domains is a general mechanism for activation of several protein kinases by second messengers (Figure 7.9A). The catalytic subunit of PKA phosphorylates serine and threonine residues of many different target proteins. Although this subunit is similar to the catalytic domains of other protein kinases, distinct amino acids allow the PKA to bind to specific target proteins, thus allowing only those targets to be phosphorylated in response to intracellular cAMP signals.
- *Ca^{2+}/calmodulin-dependent protein kinase type II (CaMKII).* Ca^{2+} ions binding to calmodulin can regulate protein phosphorylation/dephosphorylation. In neurons, the most abundant Ca^{2+}/calmodulin-dependent protein kinase is CaMKII, a multifunctional Ser/Thr protein kinase. CaMKII is composed of approximately 14 subunits, which in the brain are the α and β types. Each subunit contains a catalytic domain and a regulatory domain, as well as other domains that allow the enzyme to oligomerize and target to the proper region within the cell. Ca^{2+}/calmodulin activates CaMKII by displacing the inhibitory domain from the catalytic site (Figure 7.9B). CaMKII phosphorylates a large number of substrates, including ion channels and other proteins involved in intracellular signal transduction.
- *Protein kinase C (PKC).* Another important group of Ser/Thr protein kinases is protein kinase C (PKC). PKCs are diverse monomeric kinases activated by the second messengers DAG and Ca^{2+}. DAG causes PKC to move from the cytosol to the plasma membrane, where it also binds Ca^{2+} and phosphatidylserine, a membrane phospholipid (Figure 7.9C). These events relieve autoinhibition and cause PKC to phosphorylate various protein substrates. PKC also diffuses to sites other than the plasma membrane—such as the cytoskeleton, perinuclear sites, and the nucleus—where it phosphorylates still other substrate proteins. Prolonged activation of PKC can be accomplished with phorbol esters, tumor-promoting compounds that activate PKC by mimicking DAG.
- *Protein tyrosine kinases.* Two classes of protein kinases transfer phosphate groups to tyrosine residues on substrate proteins. Receptor tyrosine kinases are transmembrane proteins with an extracellular domain that binds to protein ligands (growth factors, neurotrophic factors, or cytokines) and an intracellular catalytic domain that phosphorylates the relevant substrate proteins. Non-receptor tyrosine kinases are cytoplasmic or membrane-associated enzymes that are indirectly activated by extracellular signals. Tyrosine phosphorylation is less common than Ser/Thr phosphorylation, and it often serves to recruit signaling molecules to the phosphorylated protein. Tyrosine

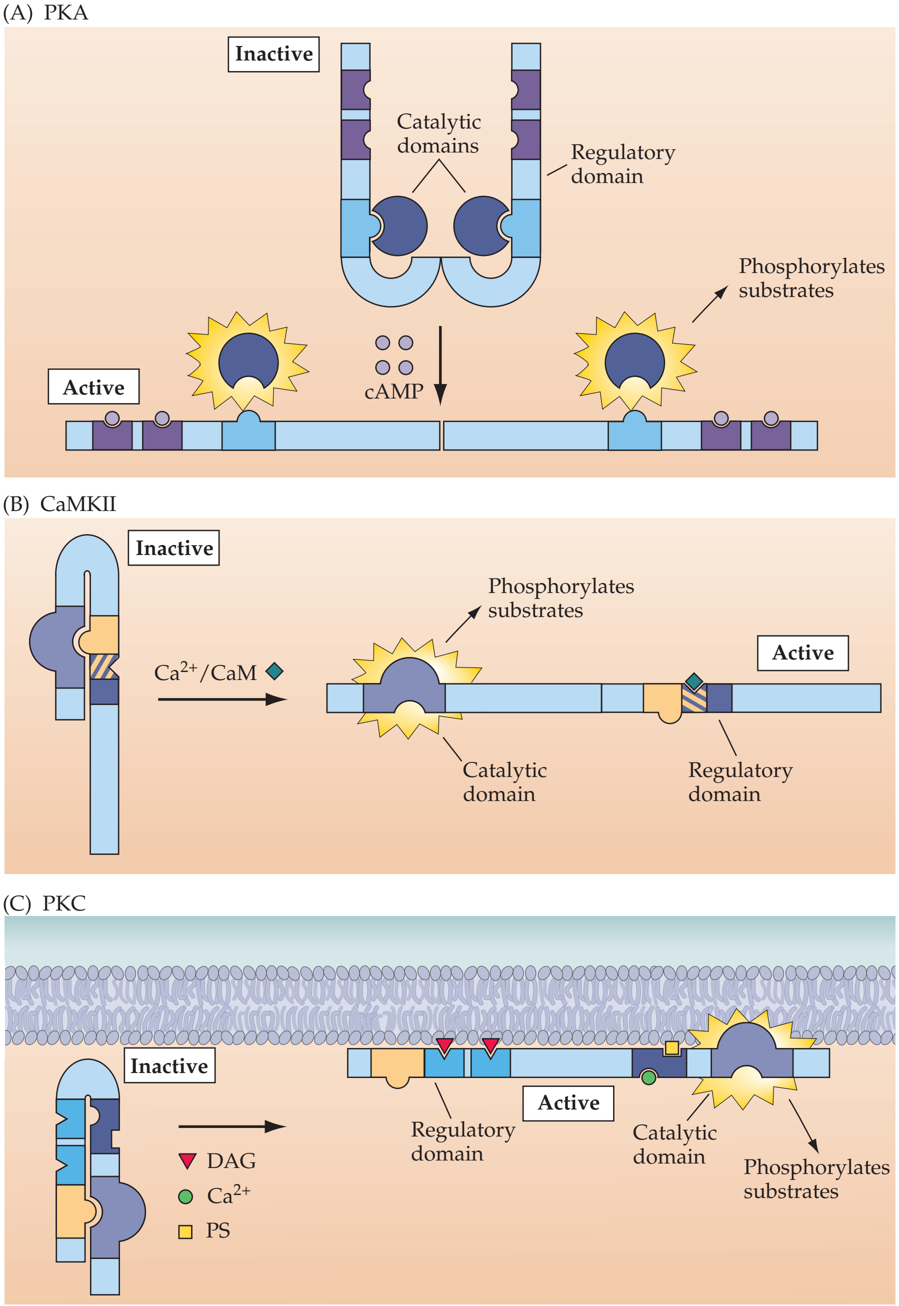

(A) PKA
Inactive
Catalytic domains
Regulatory domain
Phosphorylates substrates
Active
cAMP
(B) CaMKII
Inactive
Phosphorylates substrates
Active
Ca2+/CaM ◆
Catalytic domain
Regulatory domain
(C) PKC
Inactive
Active
Regulatory domain
Catalytic domain
Phosphorylates substrates
▼ DAG
● Ca2+
□ PS

Figure 7.9 Mechanism of activation of protein kinases. Protein kinases contain several specialized domains with specific functions. Each of the kinases has homologous catalytic domains responsible for transferring phosphate groups to substrate proteins. These catalytic domains are kept inactive by the presence of an autoinhibitory domain that occupies the catalytic site. Binding of second messengers, such as cAMP, DAG, and Ca^{2+}, to the appropriate regulatory domain of the kinase removes the autoinhibitory domain and allows the catalytic domain to be activated. For some kinases, such as PKC and CaMKII, the autoinhibitory and catalytic domains are part of the same molecule. For other kinases, such as PKA, the autoinhibitory domain is a separate subunit.

kinases are particularly important for cell growth and differentiation (see Chapters 21 and 22).

- *Mitogen-activated protein kinase (MAPK)*. In addition to protein kinases that are directly activated by second messengers, some of these molecules can be activated by other signals, such as phosphorylation by another protein kinase. Important examples of such protein kinases are the mitogen-activated protein kinases (MAPKs), also called extracellular signal-regulated kinases (ERKs). MAPKs were first identified as participants in the control of cell growth and are now known to have many other signaling functions.

MAPKs are normally inactive in neurons but become activated when they are phosphorylated by other kinases. In fact, MAPKs are part of a kinase cascade in which one protein kinase phosphorylates and activates the next protein kinase in the cascade. The extracellular signals that trigger these kinase cascades are often extracellular growth factors that bind to receptor tyrosine kinases that, in turn, activate monomeric G-proteins such as ras. Once activated, MAPKs can phosphorylate transcription factors, proteins that regulate gene expression. Among the wide variety of other MAPK substrates are various enzymes, including other protein kinases, and cytoskeletal proteins.

The best-characterized protein phosphatases are the Ser/Thr phosphatases PP1, PP2A, and PP2B (also called calcineurin). In general, protein phosphatases display less substrate specificity than protein kinases. Their limited specificity may arise from the fact that the catalytic subunits of the three major protein phosphatases are highly homologous, though each still associates with specific targeting or regulatory subunits. PP1 dephosphorylates a wide array of substrate proteins and is probably the most prevalent Ser/Thr protein phosphatase in mammalian cells. PP1 activity is regulated by several inhibitory proteins expressed in neurons. PP2A is a multisubunit enzyme with a broad range of substrates that overlap with PP1. PP2B, or calcineurin, is present at high levels in neurons. A distinctive feature of this phosphatase is its activation by Ca^{2+}/calmodulin. PP2B is composed of a catalytic and a regulatory subunit. Ca^{2+}/calmodulin activates PP2B primarily by binding to the catalytic subunit and displacing the inhibitory regulatory domain. PP2B generally does not have the same molecular targets as CaMKII, even though both enzymes are activated by Ca^{2+}/calmodulin.

In summary, activation of membrane receptors can elicit complex cascades of enzyme activation, resulting in second messenger production and protein phosphorylation or dephosphorylation. These cytoplasmic signals produce a variety of rapid physiological responses by transiently regulating enzyme activity, ion channels, cytoskeletal proteins, and many other cellular processes. In addition, such signals can propagate to the nucleus to cause long-lasting changes in gene expression.

Nuclear Signaling

Second messengers elicit prolonged changes in neuronal function by promoting the synthesis of new RNA and protein. The resulting accumulation of new proteins requires at least 30–60 minutes, a time frame that is orders of magnitude slower than the responses mediated by ion fluxes or phosphorylation. Likewise, the reversal of such events requires hours to days. In some cases, genetic “switches” can be thrown to permanently alter a neuron, as in neuronal differentiation (see Chapter 21).

The amount of protein present in cells is determined primarily by the rate of transcription of DNA into RNA (Figure 7.10). The first step in RNA synthesis is the decondensation of the structure of chromatin to provide binding sites for the RNA polymerase complex and for **transcriptional activator proteins**, also called **transcription factors**. Transcriptional activator proteins attach to binding sites that are present on the DNA molecule near the start of the target gene sequence; they also bind to other proteins that promote unwrapping of DNA. The net result of these actions is to allow RNA polymerase, an enzyme complex, to assemble on the **promoter** region of the DNA and begin transcription. In addition to clearing the promoter for RNA polymerase, activator proteins can stimulate transcription by interacting

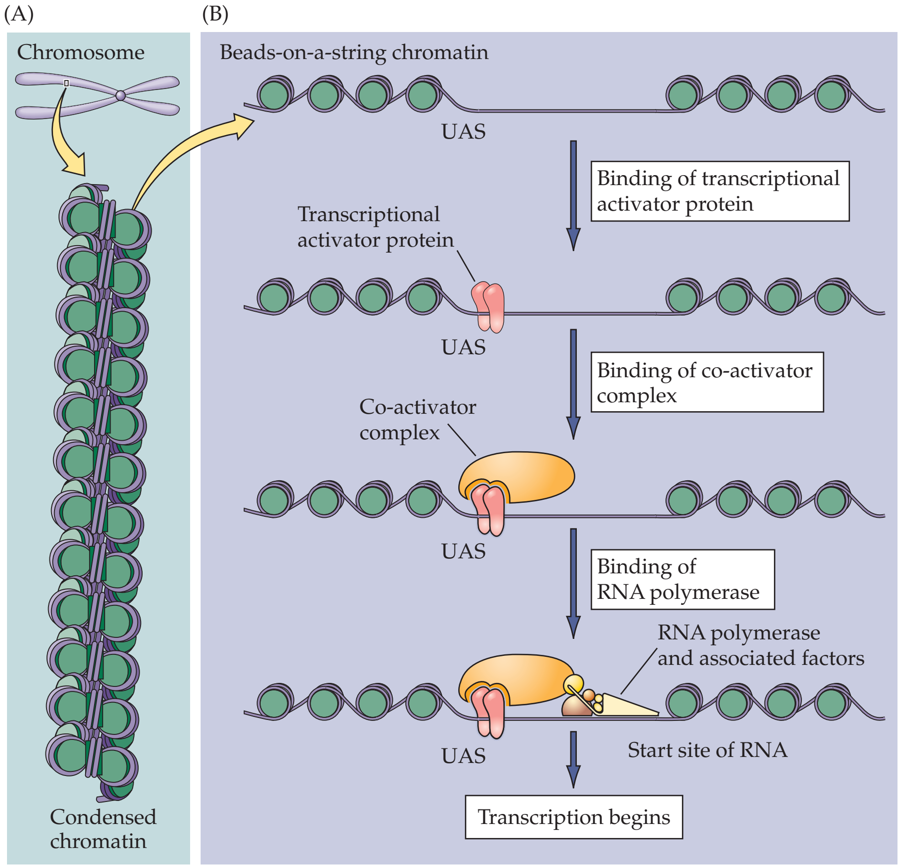

(A)
Chromosome
Condensed chromatin
(B)
Beads-on-a-string chromatin
UAS
Binding of transcriptional activator protein
Transcriptional activator protein
UAS
Binding of co-activator complex
Co-activator complex
UAS
Binding of RNA polymerase
RNA polymerase and associated factors
UAS
Start site of RNA
Transcription begins

Figure 7.10 Steps involved in transcription of DNA into RNA. Condensed chromatin (A) is decondensed into a beads-on-a-DNA-string array (B) in which an upstream activator site (UAS) is free of proteins and is bound by a sequence-specific transcriptional activator protein (transcription factor). The transcriptional activator protein then binds co-activator complexes that enable the RNA polymerase with its associated factors to bind at the start site of transcription and initiate RNA synthesis.

with the RNA polymerase complex or by interacting with other activator proteins that influence the polymerase.

Intracellular signal transduction cascades regulate gene expression by converting transcriptional activator proteins from an inactive state to an active state in which they are able to bind to DNA. This conversion comes about in several ways. The key activator proteins and the mechanisms that allow them to regulate gene expression in response to signaling events are briefly summarized in the following sections.

- *CREB.* The *c*AMP *r*esponse *e*lement *b*inding protein, usually abbreviated **CREB**, is a ubiquitous transcriptional activator (Figure 7.11). CREB is normally bound to its binding site on DNA (called the cAMP response element, or CRE), either as a homodimer or bound to another, closely related transcription factor. In unstimulated cells, CREB is not phosphorylated and has little or no transcriptional activity. However, phosphorylation of CREB greatly potentiates transcription. Several signaling pathways are capable of causing CREB to be phosphorylated. Both PKA and the ras pathway, for example, can phosphorylate CREB. CREB can also be phosphorylated in response to increased intracellular calcium, in which case the CRE site is also called the CaRE (calcium response element) site. The calcium-dependent phosphorylation of CREB is primarily caused by Ca^{2+}/calmodulin kinase IV (a relative of CaMKII) and by MAP kinase, which leads to prolonged CREB phosphorylation. CREB phosphorylation must be maintained long enough for transcription to ensue, even though neuronal electrical activity only tran-

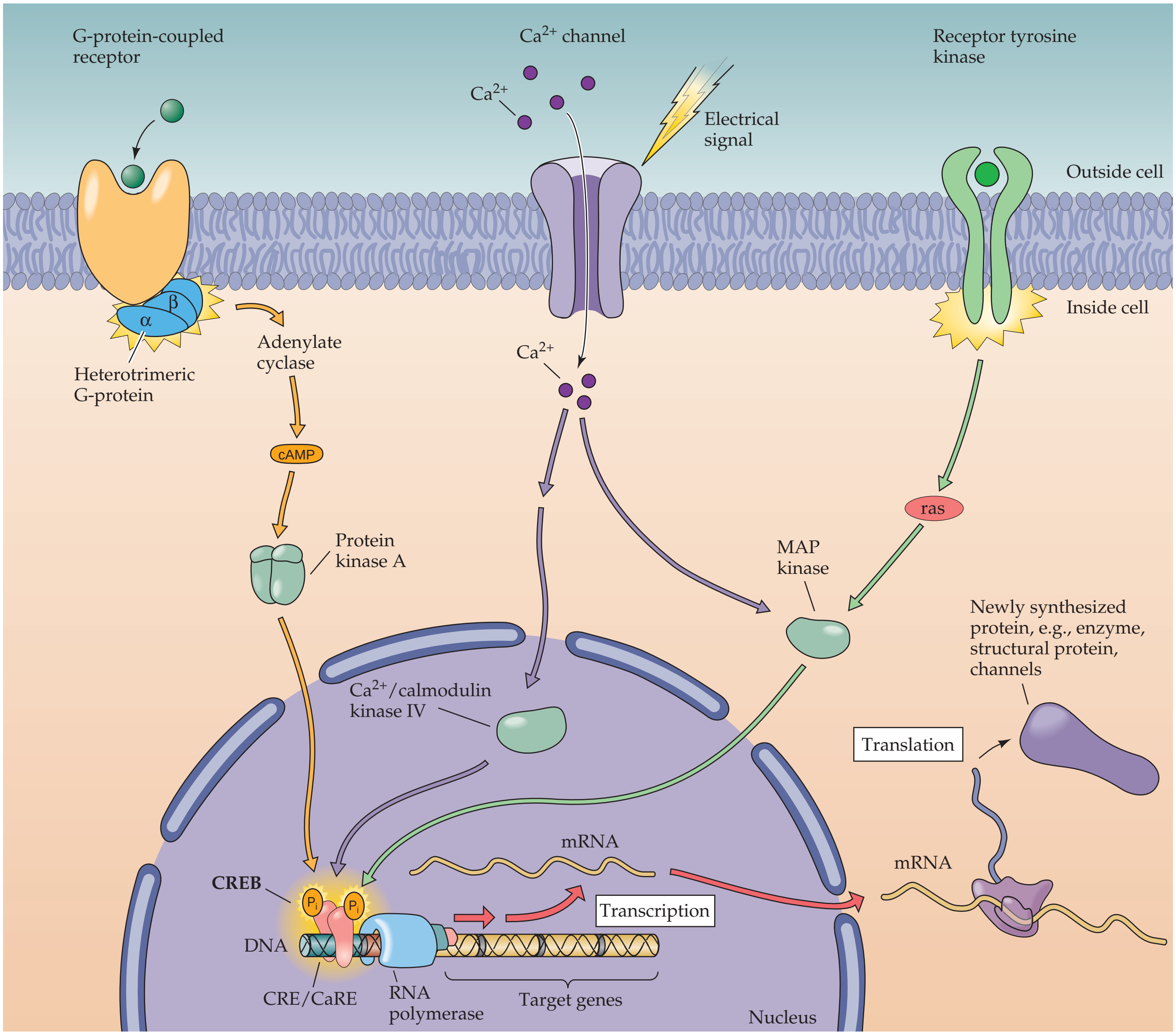

G-protein-coupled receptor
Ca^{2+} channel
Receptor tyrosine kinase
Ca^{2+}
Electrical signal
Outside cell
Inside cell
β
α
Heterotrimeric G-protein
Adenylate cyclase
Ca^{2+}
cAMP
ras
Protein kinase A
MAP kinase
Newly synthesized protein, e.g., enzyme, structural protein, channels
Ca^{2+}/calmodulin kinase IV
Translation
mRNA
mRNA
CREB
P$_i$
P$_i$
Transcription
DNA
CRE/CaRE
RNA polymerase
Target genes
Nucleus

Figure 7.11 Transcriptional regulation by CREB. Multiple signaling pathways converge by activating kinases that phosphorylate CREB. These include PKA, Ca^{2+}/calmodulin kinase IV, and MAP kinase. Phosphorylation of CREB allows it to bind co-activators (not shown in the figure), which then stimulate RNA polymerase to begin synthesis of RNA. RNA is then processed and exported to the cytoplasm, where it serves as mRNA for translation into protein.

siently raises intracellular calcium concentration. Such signaling cascades can potentiate CREB-mediated transcription by inhibiting a protein phosphatase that dephosphorylates CREB. CREB is thus an example of the convergence of multiple signaling pathways onto a single transcriptional activator.

Many genes whose transcription is regulated by CREB have been identified. CREB-sensitive genes include the immediate early gene, *c-fos* (see below), the neurotrophin BDNF (see Chapter 22), the enzyme tyrosine hydroxylase (which is important for synthesis of catecholamine neurotransmitters; see Chapter 6), and many neuropeptides (including somatostatin, enkephalin, and corticotropin releasing hormone). CREB also is thought to mediate long-lasting changes in brain function. For example, CREB has been implicated in spatial learning, behavioral sensitization, long-term memory of odorant-conditioned behavior, and long-term synaptic plasticity (see Chapters 23 and 24).

- *Nuclear receptors.* Nuclear receptors for membrane-permeant ligands also are transcriptional activators. The receptor for glucocorticoid hormones illustrates one mode of action of such receptors. In the absence of glucocorticoid hormones, the receptors are located in the cytoplasm. Binding of glucocorticoids causes the receptor to unfold and move to the nucleus, where it binds a specific recognition site on the DNA. This DNA binding activates the relevant RNA polymerase complex to initiate transcription and subsequent gene expression. Thus, a critical regulatory event for steroid receptors is their translocation to the nucleus to allow DNA binding.

The receptors for thyroid hormone (TH) and other non-steroid nuclear receptors illustrate a second mode of regulation. In the absence of TH, the receptor is bound to DNA and serves as a potent repressor of transcription. Upon binding TH, the receptor undergoes a conformational change that ultimately opens the promoter for polymerase binding. Hence, TH binding switches the receptor from being a repressor to being an activator of transcription.

- *c-fos.* A different strategy of gene regulation is apparent in the function of the transcriptional activator protein, **c-fos**. In resting cells, c-fos is present at a very low concentration. However, stimulation of the target cell causes c-fos to be synthesized, and the amount of this protein rises dramatically over 30–60 minutes. Therefore, *c-fos* is considered to be an **immediate early gene** because its synthesis is directly triggered by the stimulus. Once synthesized, c-fos protein can act as a transcriptional activator to induce synthesis of second-order genes. These are termed **delayed response genes** because their activity is delayed by the fact that an immediate early gene—*c-fos* in this case—needs to be activated first.

Multiple signals converge on *c-fos*, activating different transcription factors that bind to at least three distinct sites in the promoter region of the gene. The regulatory region of the *c-fos* gene contains a binding site that mediates transcriptional induction by cytokines and ciliary neurotropic factor. Another site is targeted by growth factors such as neurotrophins through ras and protein kinase C, and a CRE/CaRE that can bind to CREB and thereby respond to cAMP or calcium entry resulting from electrical activity. In addition to synergistic interactions among these *c-fos* sites, transcriptional signals can be integrated by converging on the same activator, such as CREB.

Nuclear signaling events typically result in the generation of a large and relatively stable complex composed of a functional transcriptional activator protein, additional proteins that bind to the activator protein, and the RNA polymerase and associated proteins bound at the start site of transcription. Most of the relevant signaling events act to “seed” this complex by generating an active transcriptional activator protein by phosphorylation, by inducing a conformational change in the activator upon ligand binding, by fostering nuclear localization, by removing an inhibitor, or simply by making more activator protein.

Examples of Neuronal Signal Transduction

Understanding the general properties of signal transduction processes at the plasma membrane, in the cytosol, and within the nucleus make it possible to consider how these processes work in concert to mediate specific functions in the brain. Three important signal transduction pathways illustrate some of the roles of intracellular signal transduction processes in the nervous system.

- *NGF/TrkA*. The first of these is signaling by the **nerve growth factor** (**NGF**). This protein is a member of the neurotrophin growth factor family and is required for the differentiation, survival, and synaptic connectivity of sympathetic and sensory neurons (see Chapter 22). NGF works by binding to a high-affinity tyrosine kinase receptor, TrkA, found on the plasma membrane of these target cells (Figure 7.12). NGF binding causes TrkA receptors to dimerize, and the intrinsic tyrosine kinase activity of each receptor then phosphorylates its partner receptor. Phosphorylated TrkA receptors trigger the ras cascade, resulting in the activation of multiple protein kinases. Some of these kinases translocate to the nucleus to activate transcriptional activators, such as CREB. This ras-based component of the NGF pathway is primarily responsible for inducing and maintaining differentiation of NGF-sensitive neurons. Phosphorylation of TrkA also causes this receptor to stimulate the activity of phospholipase C, which increases production of IP_3 and DAG. IP_3 induces release of Ca^{2+} from the endoplasmic reticulum, and diacylglycerol activates PKC. These two second messengers appear to target many of the same downstream effectors as ras. Finally, activation of TrkA receptors also causes activation of other protein kinases (such as Akt kinase) that inhibit cell death. This pathway, therefore, primarily mediates the NGF-dependent survival of sympathetic and sensory neurons described in Chapter 22.
- *Long-term depression (LTD)*. The interplay between several intracellular signals can be observed at the excitatory synapses that innervate Purkinje

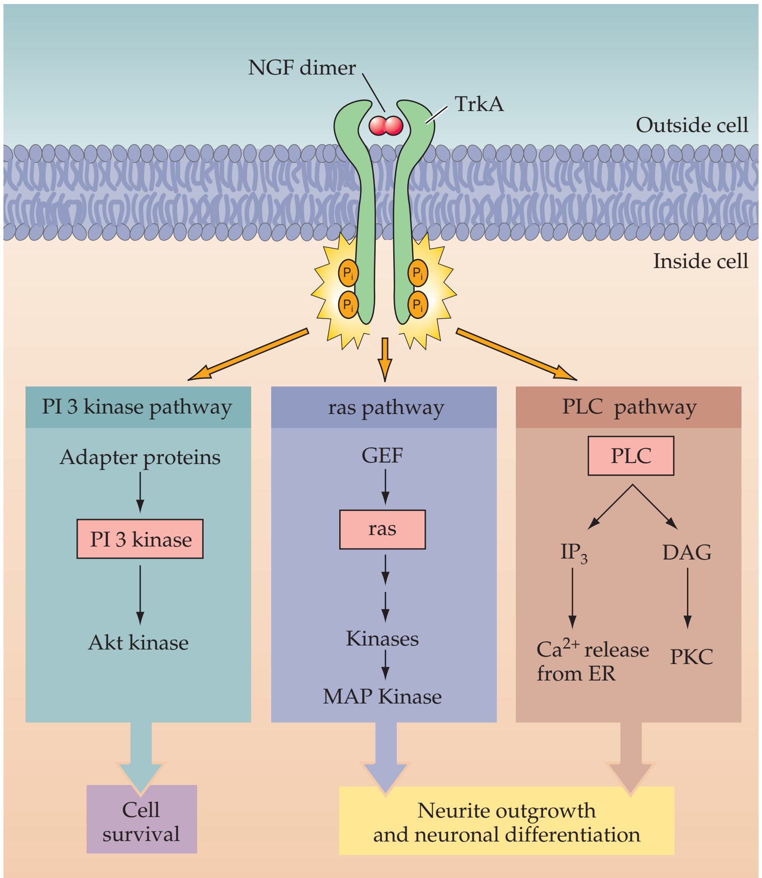


Figure 7.12 Mechanism of action of NGF. NGF binds to a high-affinity tyrosine kinase receptor, TrkA, on the plasma membrane to induce phosphorylation of TrkA at two different tyrosine residues. These phosphorylated tyrosines serve to tether various adapter proteins or phospholipase C (PLC), which, in turn, activate three major signaling pathways: the PI 3 kinase pathway leading to activation of Akt kinase, the ras pathway leading to MAP kinases, and the PLC pathway leading to release of intracellular Ca^{2+} and activation of PKC. The ras and PLC pathways primarily stimulate processes responsible for neuronal differentiation, while the PI 3 kinase pathway is primarily involved in cell survival.

cells in the cerebellum. These synapses are central to information flow through the cerebellar cortex, which in turn helps coordinate motor movements (see Chapter 18). One of the synapses is between the parallel fibers (PFs) and their Purkinje cell targets. LTD is a form of synaptic plasticity that causes the PF synapses to become less effective (see Chapter 24). When PFs are active, they release the neurotransmitter glutamate onto the dendrites of Purkinje cells. This activates AMPA-type receptors, which are ligand-gated ion channels (see Chapter 6), and causes a small EPSP that briefly depolarizes the Purkinje cell. In addition to this electrical signal, PF synaptic transmission also generates two second messengers within the Purkinje cell (Figure 7.13). The glutamate released by PFs activates metabotropic glutamate receptors, which stimulates phospholipase C to produce IP_3 and DAG. When the PF synapses alone are active, these intracellular signals are insufficient to open IP_3 receptors or to stimulate PKC.

LTD is induced when PF synapses are activated at the same time as the glutamatergic climbing fiber synapses that also innervate Purkinje cells. The climbing fiber synapses produce large EPSPs that strongly depolarize the membrane potential of the Purkinje cell. This depolarization allows Ca^{2+} to

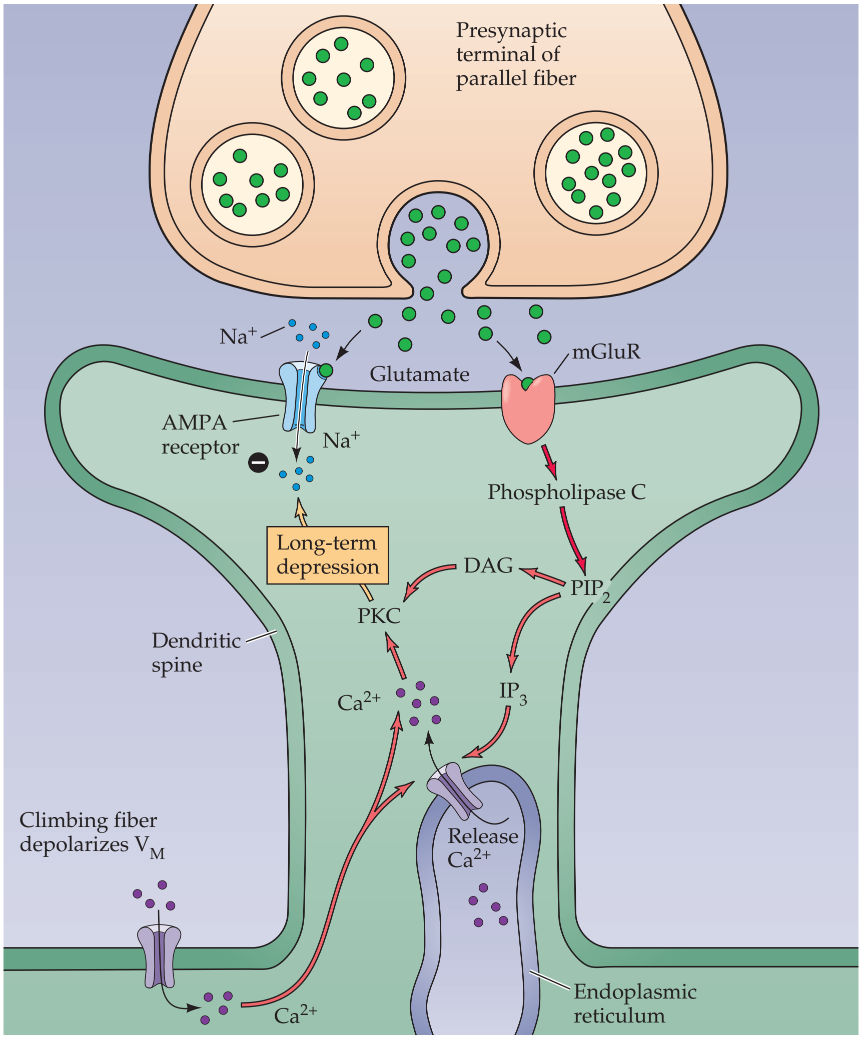

Presynaptic terminal of parallel fiber
Na^+
Glutamate
mGluR
AMPA receptor
Na^+
Phospholipase C
Long-term depression
DAG
PIP_2
PKC
Dendritic spine
Ca^{2+}
IP_3
Climbing fiber depolarizes V_M
Release Ca^{2+}
Endoplasmic reticulum
Ca^{2+}

Figure 7.13 Signaling at cerebellar parallel fiber synapses. Glutamate released by parallel fibers activates both AMPA-type and metabotropic receptors. The latter produces IP_3 and DAG within the Purkinje cell. When paired with a rise in Ca^{2+} associated with activity of climbing fiber synapses, the IP_3 causes Ca^{2+} to be released from the endoplasmic reticulum, while Ca^{2+} and DAG together activate protein kinase C. These signals together change the properties of AMPA receptors to produce LTD.

enter the Purkinje cell via voltage-gated Ca^{2+} channels. When both synapses are simultaneously activated, the rise in intracellular Ca^{2+} concentration caused by the climbing fiber synapse enhances the sensitivity of IP_3 receptors to the IP_3 produced by PF synapses and allows the IP_3 receptors within the Purkinje cell to open. This releases Ca^{2+} from the endoplasmic reticulum and further elevates Ca^{2+} concentration locally near the PF synapses. This larger rise in Ca^{2+}, in conjunction with the DAG produced by the PF synapses, activates PKC. PKC in turn phosphorylates a number of substrate proteins. Ultimately, these signaling processes change AMPA-type receptors at the PF synapse, so that these receptors produce smaller electrical signals in response to the glutamate released from the PFs. This weakening of the PF synapse is the final cause of LTD.

In short, transmission at Purkinje cell synapses produces brief electrical signals and chemical signals that last much longer. The temporal interplay between these signals allows LTD to occur only when both PF and climbing fiber synapses are active. The actions of IP_3, DAG and Ca^{2+} also are restricted to small parts of the Purkinje cell dendrite, which is a more limited spatial range than the EPSPs, which spread throughout the entire dendrite and cell body of the Purkinje cell. Thus, in contrast to the electrical signals, the second messenger signals can impart precise information about the location of active synapses and allow LTD to occur only in the vicinity of active PFs.

- *Phosphorylation of tyrosine hydroxylase*. A third example of intracellular signaling in the nervous system is the regulation of the enzyme tyrosine hydroxylase. Tyrosine hydroxylase governs the synthesis of the catecholamine neurotransmitters: dopamine, norepinephrine, and epinephrine (see Chapter 6). A number of signals, including electrical activity, other neurotransmitters, and NGF, increase the rate of catecholamine synthesis by increasing the catalytic activity of tyrosine hydroxylase (Figure 7.14). The rapid increase of tyrosine hydroxylase activity is largely due to phosphorylation of this enzyme.

Tyrosine hydroxylase is a substrate for several protein kinases, including PKA, CaMKII, MAP kinase, and PKC. Phosphorylation causes conformational changes that increase the catalytic activity of tyrosine hydroxylase. Stimuli that elevate cAMP, Ca^{2+}, or DAG can all increase tyrosine hydroxylase activity and thus increase the rate of catecholamine biosynthesis. This regulation by several different signals allows for close control of tyrosine hydroxylase activity, and illustrates how several different pathways can converge to influence a key enzyme involved in synaptic transmission.

Summary

A diversity of signal transduction pathways exist within all neurons. Activation of these pathways typically is initiated by chemical signals such as neurotransmitters and hormones. These molecules bind to receptors that include ligand-gated ion channels, G-protein-coupled receptors and tyrosine kinase receptors. Many of these receptors activate either heterotrimeric or monomeric G-proteins that regulate intracellular enzyme cascades and/or ion channels. A common outcome of the activation of these receptors is the production of second messengers, such as cAMP, Ca^{2+}, and IP_3, that bind to effector enzymes. Particularly important effectors are protein kinases and phosphatases that regulate the phosphorylation state of their substrates, and thus their function. These substrates can be metabolic enzymes or other signal transduction molecules, such as ion channels, protein kinases, or transcription factors that regulate gene expression. Examples of transcription

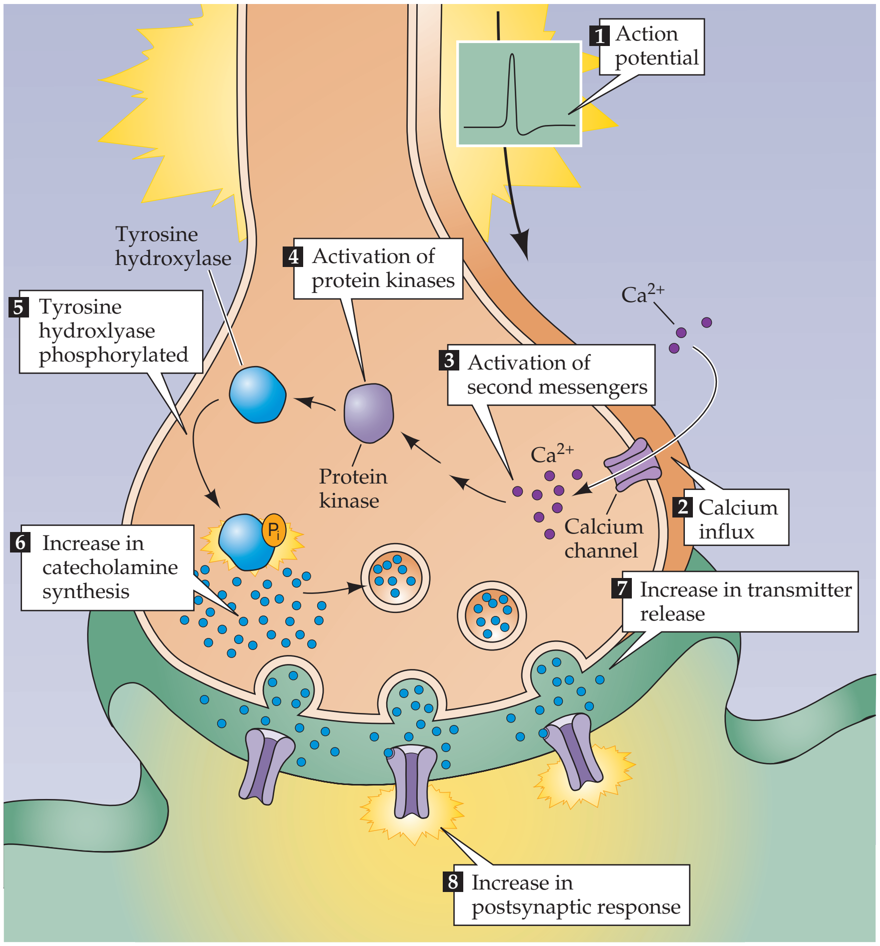

1 Action potential
Tyrosine hydroxylase
4 Activation of protein kinases
Ca2+
5 Tyrosine hydroxlyase phosphorylated
3 Activation of second messengers
Ca2+
Protein kinase
Pi
Calcium channel
2 Calcium influx
6 Increase in catecholamine synthesis
7 Increase in transmitter release
8 Increase in postsynaptic response

Figure 7.14 Regulation of tyrosine hydroxylase by protein phosphorylation. This enzyme governs the synthesis of the catecholamine neurotransmitters and is stimulated by a number of intracellular signals. In the example shown here, neuronal electrical activity (1) causes influx of Ca^{2+} (2). The resultant rise in intracellular Ca^{2+} concentration (3) activates protein kinases (4), which phosphorylates tyrosine hydroxylase (5) to stimulate catecholamine synthesis (6). This, in turn, increases release of catecholamines (7) and enhances the postsynaptic response produced by the synapse (8).

factors include CREB, steroid hormone receptors, and c-fos. This plethora of molecular components allows intracellular signal transduction pathways to generate responses over a wide range of times and distances, greatly augmenting and refining the information-processing ability of neuronal circuits and ultimately systems.

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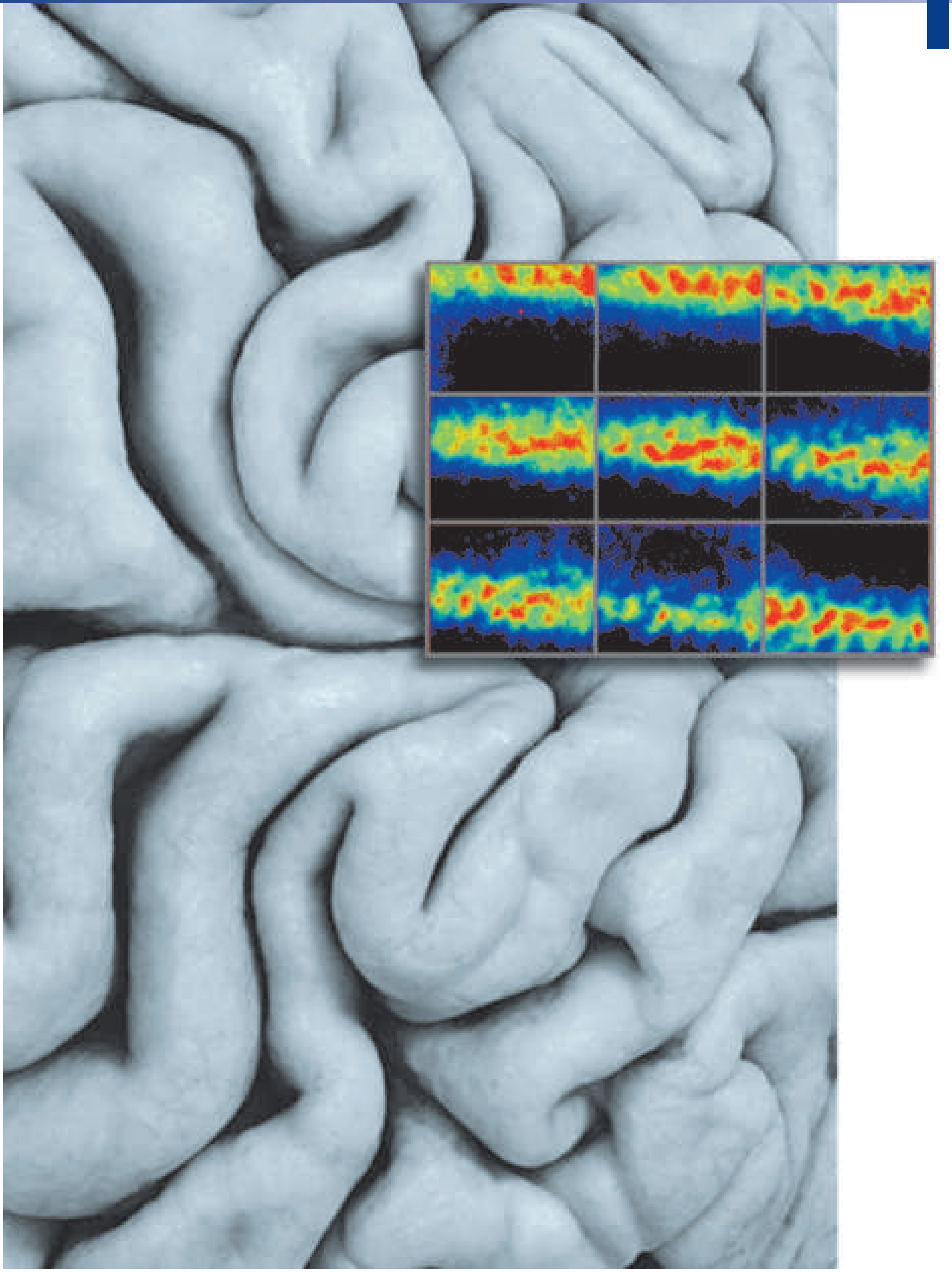
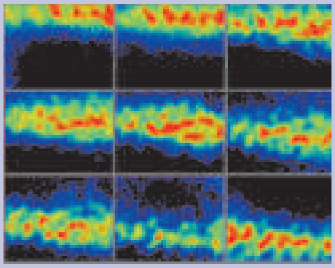
Sensation and Sensory Processing

II





Surface view of the primary visual cortex illustrating patterns of neural activity visualized with intrinsic signal optical imaging techniques (see Box C in Chapter 11). Each panel illustrates the activity evoked by viewing a single thin vertical line. The smooth progression of the activated region from the upper left to the lower right panel illustrates the orderly mapping of visual space. The patchy appearance of the activated region in each panel reflects the columnar mapping of orientation preference. Red regions are the most active, black the least. (Courtesy of Bill Bosking, Justin Crowley, Tom Tucker, and David Fitzpatrick.)

UNIT II

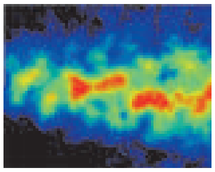
SENSATION AND SENSORY PROCESSING

8 The Somatic Sensory System
9 Pain
10 Vision: The Eye
11 Central Visual Pathways
12 The Auditory System
13 The Vestibular System
14 The Chemical Senses

Sensation entails the ability to transduce, encode, and ultimately perceive information generated by stimuli arising from both the external and internal environments. Much of the brain is devoted to these tasks. Although the basic senses—somatic sensation, vision, audition, vestibular sensation, and the chemical senses—are very different from one another, a few fundamental rules govern the way the nervous system deals with each of these diverse modalities. Highly specialized nerve cells called receptors convert the energy associated with mechanical forces, light, sound waves, odorant molecules, or ingested chemicals into neural signals—afferent sensory signals—that convey information about the stimulus to the brain. Afferent sensory signals activate central neurons capable of representing both the qualitative and quantitative aspects of the stimulus (what it is and how strong it is) and, in some modalities (somatic sensation, vision, and audition) the location of the stimulus in space (where it is).

The clinical evaluation of patients routinely requires an assessment of the sensory systems to infer the nature and location of potential neurological problems. Knowledge of where and how the different sensory modalities are transduced, relayed, represented, and further processed to generate appropriate behavioral responses is therefore essential to understanding and treating a wide variety of diseases. Accordingly, these chapters on the neurobiology of sensation also introduce some of the major structure/function relationships in the sensory components of the nervous system.

Chapter 8



The Somatic Sensory System

Overview

The somatic sensory system has two major components: a subsystem for the detection of mechanical stimuli (e.g., light touch, vibration, pressure, and cutaneous tension), and a subsystem for the detection of painful stimuli and temperature. Together, these two subsystems give humans and other animals the ability to identify the shapes and textures of objects, to monitor the internal and external forces acting on the body at any moment, and to detect potentially harmful circumstances. This chapter focuses on the mechanosensory subsystem; the pain and temperature subsystem is taken up in the following chapter.

Mechanosensory processing of external stimuli is initiated by the activation of a diverse population of cutaneous and subcutaneous mechanoreceptors at the body surface that relays information to the central nervous system for interpretation and ultimately action. Additional receptors located in muscles, joints, and other deep structures monitor mechanical forces generated by the musculoskeletal system and are called proprioceptors. Mechanosensory information is carried to the brain by several ascending pathways that run in parallel through the spinal cord, brainstem, and thalamus to reach the primary somatic sensory cortex in the postcentral gyrus of the parietal lobe. The primary somatic sensory cortex projects in turn to higher-order association cortices in the parietal lobe, and back to the subcortical structures involved in mechanosensory information processing.

Cutaneous and Subcutaneous Somatic Sensory Receptors

The specialized sensory receptors in the cutaneous and subcutaneous tissues are dauntingly diverse (Table 8.1). They include free nerve endings in the skin, nerve endings associated with specializations that act as amplifiers or filters, and sensory terminals associated with specialized transducing cells that influence the ending by virtue of synapse-like contacts. Based on function, this variety of receptors can be divided into three groups: **mechanoreceptors**, **nociceptors**, and **thermoceptors**. On the basis of their morphology, the receptors near the body surface can also be divided into **free** and **encapsulated** types. Nociceptor and thermoceptor specializations are referred to as **free nerve endings** because the unmyelinated terminal branches of these neurons ramify widely in the upper regions of the dermis and epidermis (as well as in some deeper tissues); their role in pain and temperature sensation is discussed in Chapter 9. Most other cutaneous receptors show some degree of **encapsulation**, which helps determine the nature of the stimuli to which they respond.

Despite their variety, all somatic sensory receptors work in fundamentally the same way: Stimuli applied to the skin deform or otherwise change the

TABLE 8.1

The Major Classes of Somatic Sensory Receptors

Receptor type	*Anatomical characteristics*	*Associated axons[a] (and diameters)*	*Axonal conduction velocities*	*Location*	*Function*	*Rate of adaptation*	*Threshold of activation*
Free nerve endings	Minimally specialized nerve endings	C, Aδ	2–20 m/s	All skin	Pain, temperature, crude touch	Slow	High
Meissner's corpuscles	Encapsulated; between dermal papillae	Aβ 6–12 μm		Principally glabrous skin	Touch, pressure (dynamic)	Rapid	Low
Pacinian corpuscles	Encapsulated; onionlike covering	Aβ 6–12 μm		Subcutaneous tissue, interosseous membranes, viscera	Deep pressure, vibration (dynamic)	Rapid	Low
Merkel's disks	Encapsulated; associated with peptide-releasing cells	Aβ		All skin, hair follicles	Touch, pressure (static)	Slow	Low
Ruffini's corpuscles	Encapsulated; oriented along stretch lines	Aβ 6–12 μm		All skin	Stretching of skin	Slow	Low
Muscle spindles	Highly specialized (see Figure 8.5 and Chapter 15)	Ia and II		Muscles	Muscle length	Both slow and rapid	Low
Golgi tendon organs	Highly specialized (see Chapter 15)	Ib		Tendons	Muscle tension	Slow	Low
Joint receptors	Minimally specialized	—		Joints	Joint position	Rapid	Low

[a] In the 1920s and 1930s, there was a virtual cottage industry classifying axons according to their conduction velocity. Three main categories were discerned, called A, B, and C. A comprises the largest and fastest axons, C the smallest and slowest. Mechanoreceptor axons generally fall into category A. The A group is further broken down into subgroups designated *α* (the fastest), *β*, and *δ* (the slowest). To make matters even more confusing, muscle afferent axons are usually classified into four additional groups—I (the fastest), II, III, and IV (the slowest)—with subgroups designated by lowercase roman letters!

nerve endings, which in turn affects the ionic permeability of the receptor cell membrane. Changes in permeability generate a depolarizing current in the nerve ending, thus producing a **receptor** (or **generator**) **potential** that triggers action potentials, as described in Chapters 2 and 3. This overall process, in which the energy of a stimulus is converted into an electrical signal in the sensory neuron, is called **sensory transduction** and is the critical first step in all sensory processing.

The *quality* of a mechanosensory (or any other) stimulus (i.e., what it represents and where it is) is determined by the properties of the relevant receptors and the location of their central targets (Figure 8.1). The quantity or strength of the stimulus is conveyed by the rate of action potential discharge triggered by the receptor potential (although this relationship is nonlinear and often quite complex). Some receptors fire rapidly when a stimulus is first presented and then fall silent in the presence of continued stimulation (which is to say they "adapt" to the stimulus), whereas others generate a sustained discharge in the presence of an ongoing stimulus (Figure 8.2). The usefulness of having some receptors that adapt quickly and others that do not is to provide information about both the *dynamic* and *static* qualities of a stimulus. Receptors that initially fire in the presence of a stimulus and then

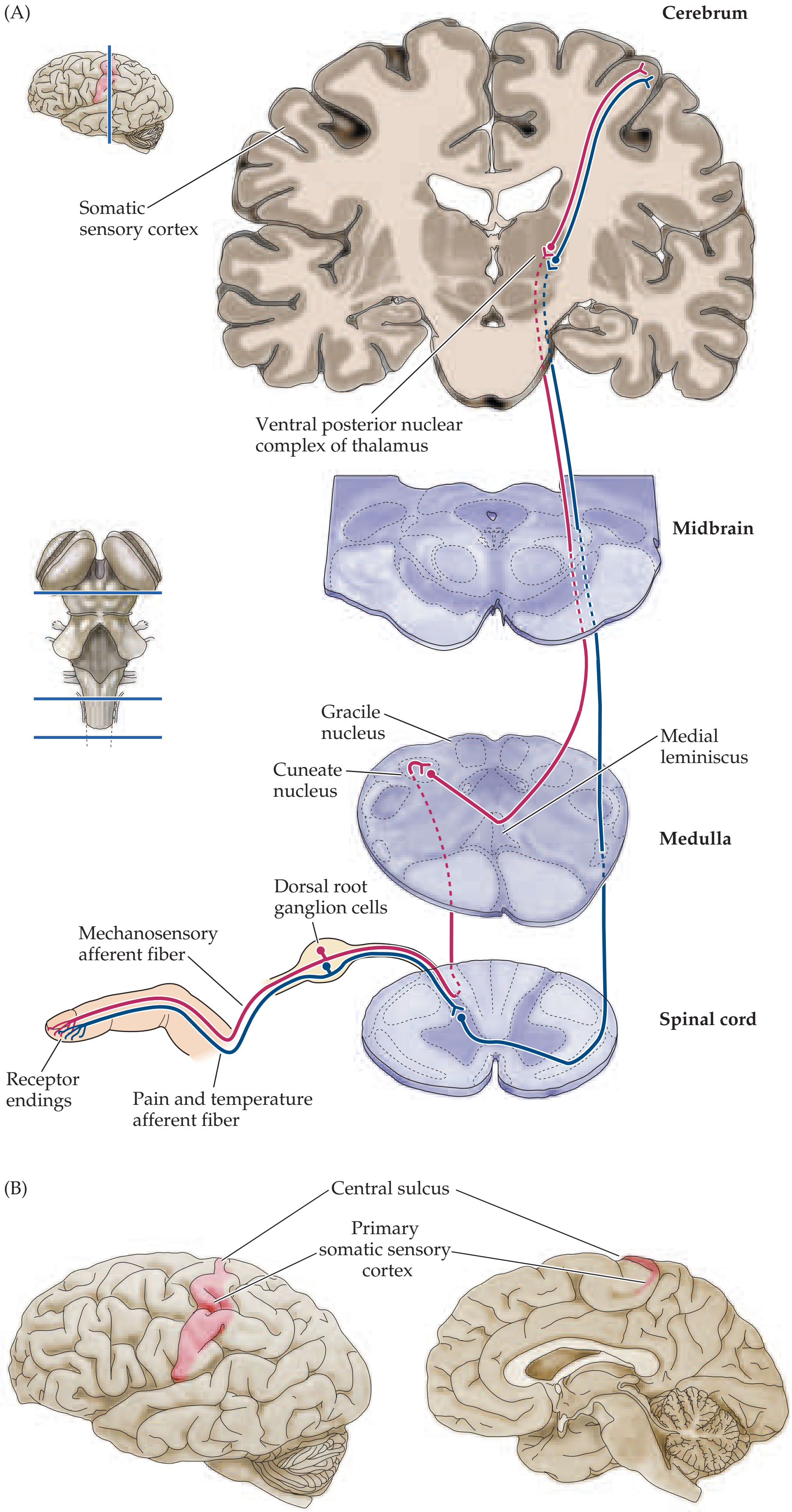

(A)
Cerebrum
Somatic sensory cortex
Ventral posterior nuclear complex of thalamus
Midbrain
Gracile nucleus
Cuneate nucleus
Medial leminiscus
Medulla
Dorsal root ganglion cells
Mechanosensory afferent fiber
Spinal cord
Receptor endings
Pain and temperature afferent fiber
(B)
Central sulcus
Primary somatic sensory cortex

Figure 8.1 General organization of the somatic sensory system. (A) Mechanosensory information about the body reaches the brain by way of a three-neuron relay (shown in red). The first synapse is made by the terminals of the centrally projecting axons of dorsal root ganglion cells onto neurons in the brainstem nuclei (the local branches involved in segmental spinal reflexes are not shown here). The axons of these second-order neurons synapse on third-order neurons of the ventral posterior nuclear complex of the thalamus, which in turn send their axons to the primary somatic sensory cortex (red). Information about pain and temperature takes a different course (shown in blue; the anterolateral system), and is discussed in the following chapter. (B) Lateral and midsagittal views of the human brain, illustrating the approximate location of the primary somatic sensory cortex in the anterior parietal lobe, just posterior to the central sulcus.

sylvius

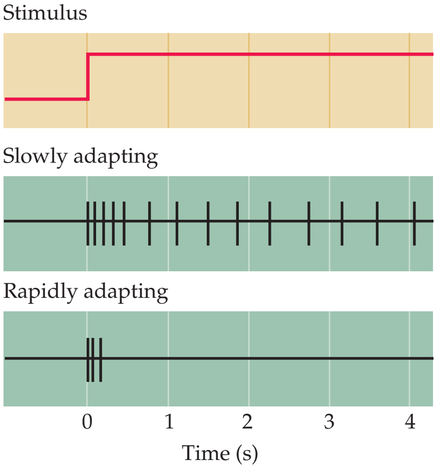


Figure 8.2 Slowly adapting mechanoreceptors continue responding to a stimulus, whereas rapidly adapting receptors respond only at the onset (and often the offset) of stimulation. These functional differences allow the mechanoreceptors to provide information about both the static (via slowly adapting receptors) and dynamic (via rapidly adapting receptors) qualities of a stimulus.

become quiescent are particularly effective in conveying information about changes in the information the receptor reports; conversely, receptors that continue to fire convey information about the persistence of a stimulus. Accordingly, somatic sensory receptors and the neurons that give rise to them are usually classified into rapidly or slowly adapting types (see Table 8.1). **Rapidly adapting**, or **phasic**, receptors respond maximally but briefly to stimuli; their response decreases if the stimulus is maintained. Conversely, **slowly adapting**, or **tonic**, receptors keep firing as long as the stimulus is present.

Mechanoreceptors Specialized to Receive Tactile Information

Four major types of encapsulated mechanoreceptors are specialized to provide information to the central nervous system about touch, pressure, vibration, and cutaneous tension: Meissner's corpuscles, Pacinian corpuscles, Merkel's disks, and Ruffini's corpuscles (Figure 8.3 and Table 8.1). These receptors are referred to collectively as **low-threshold** (or high-sensitivity) mechanoreceptors because even weak mechanical stimulation of the skin induces them to produce action potentials. All low-threshold mechanoreceptors are innervated by relatively large myelinated axons (type Aβ; see Table 8.1), ensuring the rapid central transmission of tactile information.

Meissner's corpuscles, which lie between the dermal papillae just beneath the epidermis of the fingers, palms, and soles, are elongated receptors formed by a connective tissue capsule that comprises several lamellae of Schwann cells. The center of the capsule contains one or more afferent nerve fibers that generate rapidly adapting action potentials following minimal skin depression. Meissner's corpuscles are the most common mechanoreceptors of "glabrous" (smooth, hairless) skin (the fingertips, for instance), and their afferent fibers account for about 40% of the sensory innervation of the human hand. These corpuscles are particularly efficient in transducing information about the relatively low-frequency vibrations (30–50 Hz) that occur when textured objects are moved across the skin.

Pacinian corpuscles are large encapsulated endings located in the subcutaneous tissue (and more deeply in interosseous membranes and mesenteries of the gut). These receptors differ from Meissner's corpuscles in their morphology, distribution, and response threshold. The Pacinian corpuscle has an onion-like capsule in which the inner core of membrane lamellae is separated from an outer lamella by a fluid-filled space. One or more rapidly adapting afferent axons lie at the center of this structure. The capsule again acts as a filter, in this case allowing only transient disturbances at high frequencies (250–350 Hz) to activate the nerve endings. Pacinian corpuscles adapt more rapidly than Meissner's corpuscles and have a lower response threshold. These attributes suggest that Pacinian corpuscles are involved in the discrimination of fine surface textures or other moving stimuli that produce high-frequency vibration of the skin. In corroboration of this supposition, stimulation of Pacinian corpuscle afferent fibers in humans induces a sensation of vibration or tickle. They make up 10–15% of the cutaneous receptors in the hand. Pacinian corpuscles located in interosseous membranes probably detect vibrations transmitted to the skeleton. Structurally similar endings found in the bills of ducks and geese and in the legs of cranes and herons detect vibrations in water; such endings in the wings of soaring birds detect vibrations produced by air currents. Because they are rapidly adapting, Pacinian corpuscles, like Meissner's corpuscles, provide information primarily about the dynamic qualities of mechanical stimuli.

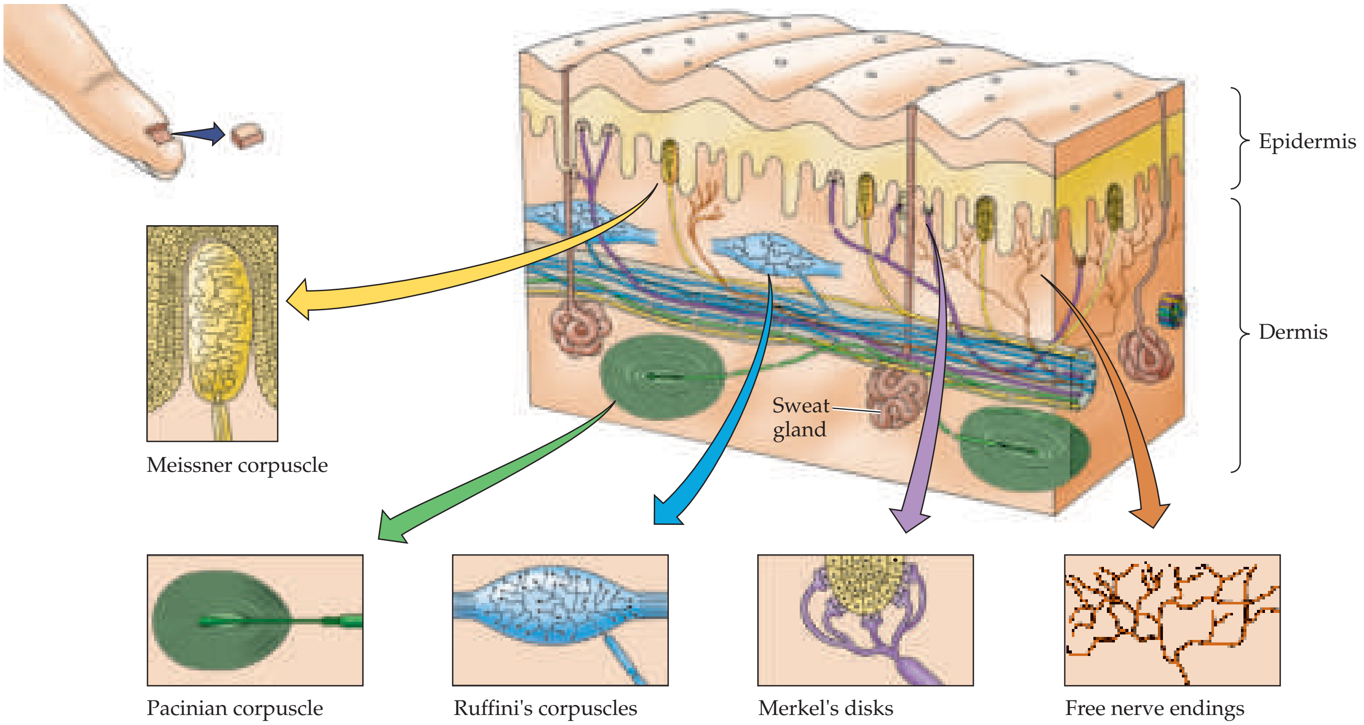


Figure 8.3 The skin harbors a variety of morphologically distinct mechanoreceptors. This diagram represents the smooth, hairless (also called glabrous) skin of the fingertip. The major characteristics of the various receptor types are summarized in Table 8.1. (After Darian-Smith, 1984.)

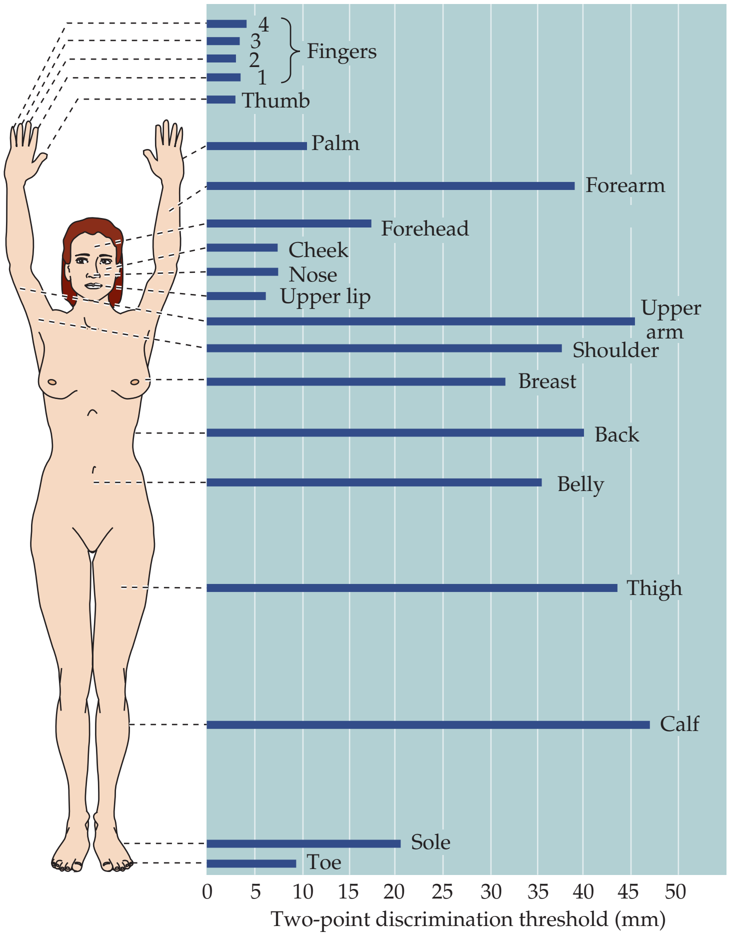
Slowly adapting cutaneous mechanoreceptors include **Merkel's disks** and **Ruffini's corpuscles** (see Figure 8.3 and Table 8.1). Merkel's disks are located in the epidermis, where they are precisely aligned with the papillae that lie beneath the dermal ridges. They account for about 25% of the mechanoreceptors of the hand and are particularly dense in the fingertips, lips, and external genitalia. The slowly adapting nerve fiber associated with each Merkel's disk enlarges into a saucer-shaped ending that is closely applied to another specialized cell containing vesicles that apparently release peptides that modulate the nerve terminal. Selective stimulation of these receptors in humans produces a sensation of light pressure. These several properties have led to the supposition that Merkel's disks play a major role in the static discrimination of shapes, edges, and rough textures.

Ruffini's corpuscles, although structurally similar to other tactile receptors, are not well understood. These elongated, spindle-shaped capsular specializations are located deep in the skin, as well as in ligaments and tendons. The long axis of the corpuscle is usually oriented parallel to the stretch lines in skin; thus, Ruffini's corpuscles are particularly sensitive to the cutaneous stretching produced by digit or limb movements. They account for about 20% of the receptors in the human hand and do not elicit any particular tactile sensation when stimulated electrically. Although there is still some question as to their function, they probably respond primarily to internally generated stimuli (see the section on proprioception, below).

Differences in Mechanosensory Discrimination across the Body Surface

The accuracy with which tactile stimuli can be sensed varies from one region of the body to another, a phenomenon that illustrates some further principles

Figure 8.4 Variation in the sensitivity of tactile discrimination as a function of location on the body surface, measured here by two-point discrimination. (After Weinstein, 1968.)



of somatic sensation. Figure 8.4 shows the results of an experiment in which variation in tactile ability across the body surface was measured by **two-point discrimination**. This technique measures the minimal interstimulus distance required to perceive two simultaneously applied stimuli as distinct (the indentations of the points of a pair of calipers, for example). When applied to the skin, such stimuli of the fingertips are discretely perceived if they are only 2 mm apart. In contrast, the same stimuli applied to the forearm are not perceived as distinct until they are at least 40 mm apart! This marked regional difference in tactile ability is explained by the fact that the encapsulated mechanoreceptors that respond to the stimuli are three to four times more numerous in the fingertips than in other areas of the hand, and many times more dense than in the forearm. Equally important in this regional difference are the sizes of the neuronal receptive fields. The **receptive** field of a somatic sensory neuron is the region of the skin within which a tactile stimulus evokes a sensory response in the cell or its axon (Boxes A and B). Analysis of the human hand shows that the receptive fields of mechanosensory neurons are 1–2 mm in diameter on the fingertips but 5–10 mm on the palms. The receptive fields on the arm are larger still. The importance of receptive field size is easy to envision. If, for instance, the receptive fields of all cutaneous receptor neurons covered the entire digital pad, it would be impossible to discriminate two spatially separate stimuli applied to the fingertip (since all the receptive fields would be returning the same spatial information).

Box A

Receptive Fields and Sensory Maps in the Cricket

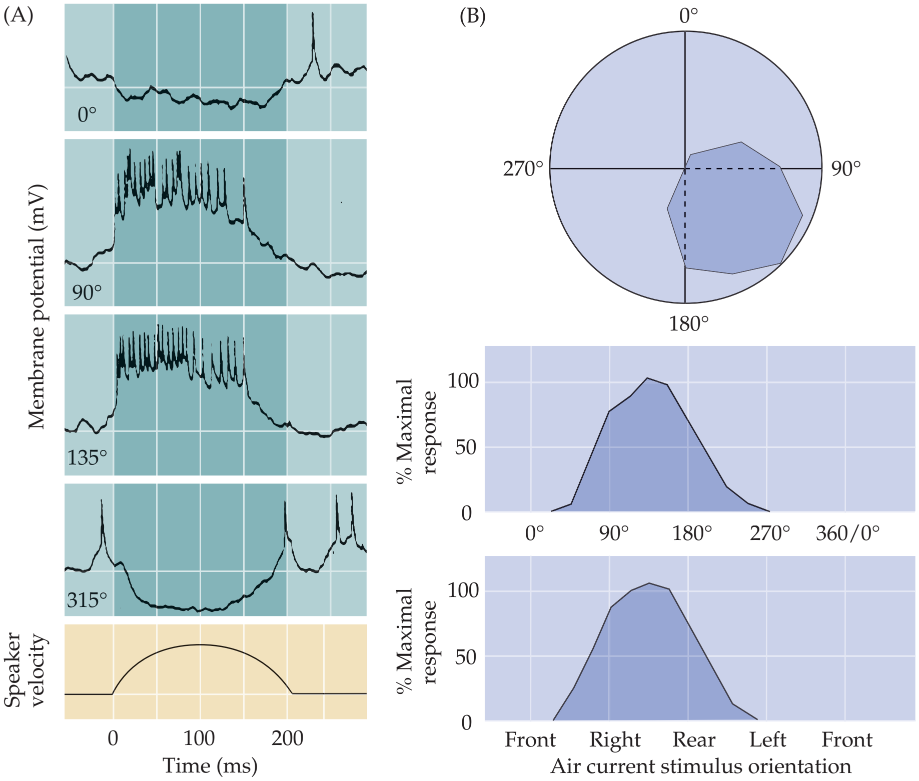
Two principles of somatiosensory organization have emerged from studies of the mammalian brain: (1) individual neurons are tuned to particular aspects of complex stimuli; and (2) these stimulus qualities are represented in an orderly fashion in relevant regions of the nervous system. These principles apply equally well to invertebrates, including the equivalent of the somatic sensory system in insects such as crickets, grasshoppers, and cockroaches.

In the cricket, the salient tactile stimulation for the animal comes from air currents that displace sensory hairs of bilaterally symmetric sensory structures called cerci (sing. *cercus*). The location and structure of specific cercal hairs allow them to be displaced by air currents having different directions and speeds (Figure A). Accordingly, the peripheral sensory neurons associated with the hairs represent the full range of air current directions and velocities impinging on the animal. This information is carried centrally and is systematically represented in a region of the cricket central nervous system called the terminal ganglion.

Individual neurons in this ganglion correspond to the cercal hairs, and have receptive fields and response properties that represent a full range of directions and speeds for extrinsic mechanical forces, including air currents (Figure B). For the cricket, the significance of this information is, among other things, detecting the direction and speed of oncoming objects to then execute motor programs for escape. (This is also the likely significance of this representation for cockroaches, which can therefore escape the consequences of a descending human foot.)

Much like the somatic sensory system in mammals, the primary sensory afferents project to the terminal ganglion in an orderly fashion, such that there is a somatotopic map of air current directions. And, like mammals, individual neurons within this representation are tuned to specific aspects of the mechanical forces acting on the cricket.

These facts about insects' mechanosensory system emphasize that somatic sensory functions are basically similar across a wide range of animals. Indeed, regardless of sensory modality, nervous system organization, or the identity of the organism, it is likely that stimulus specificity will be reflected in receptive fields of individual neurons and there will be orderly mapping of those receptive fields into either a topographic or computational map in the animal's brain.



(A) Intracellular recording of action potential activity of an individual sensory neuron's responses to different directions of wind current. (B) The plots indicate this neuron's receptive field for wind direction (top) and the tuning curve for the neuron's selective firing to its preferred direction. (After Miller et al., 1991.)

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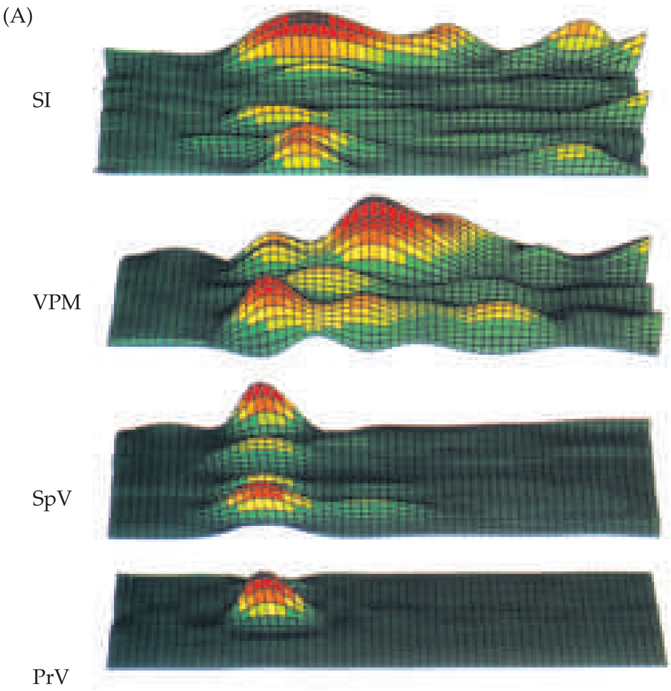
Box B

Dynamic Aspects of Somatic Sensory Receptive Fields

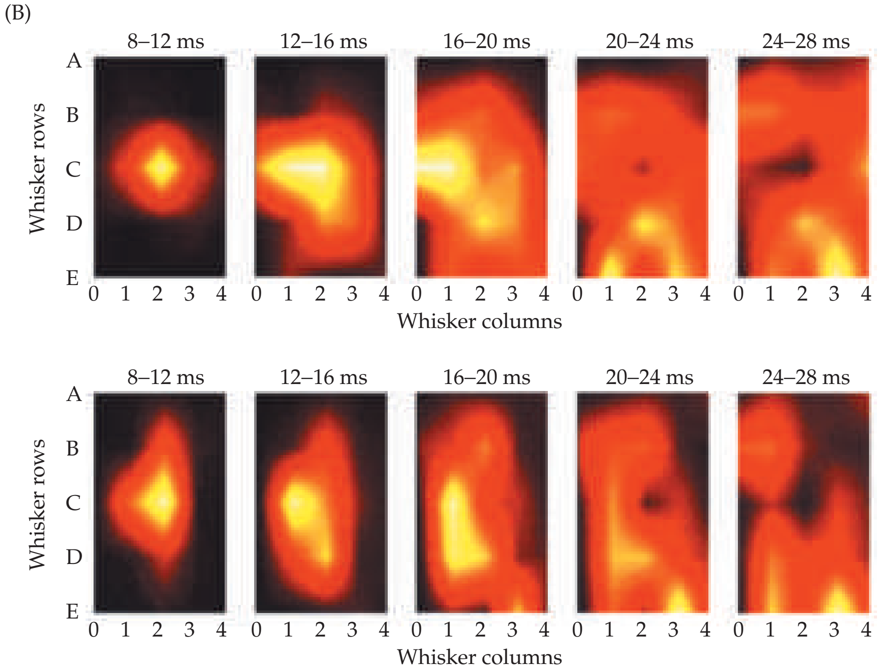
When humans explore objects with their hands, multiple contacts between the skin and the object surface generate extraordinarily complex patterns of tactile stimuli. As a consequence, the somatic sensory system must process signals that change continuously in time. Nonetheless, we routinely discriminate the size, texture and shape of objects with great accuracy. Until recently, the temporal structure of such stimuli was not considered a major variable in characterizing the physiological properties of somatic sensory neurons. For instance, the classical definition of the receptive field of a somatic sensory neuron takes into account only the overall area of the body surface that elicits significant variation in the neuron's firing rate. By the same token, the topographic maps in the somatic sensory system have been interpreted as evidence that tactile information processing involves primarily spatial criteria.

The advent of multiple electrode recording to simultaneously monitor the activity of large populations of single neurons has begun to change this "static" view of the somatic sensory system. In both primates and rodents, this approach has shown that the receptive fields of cortical and subcortical neurons



(A) Simultaneous electrode recordings in behaving rats allow monitoring of the spatiotemporal spread of neuronal activation across several levels of the somatic sensory system following stimulation (of a single facial whisker, in this example). These 3-D graphs represent patterns of neuronal ensemble activity at each level of the pathway. The x axis represents the poststimulus time in ms, the y axis the number of neurons recorded at each level; the color-coded gradient in the z axis shows the response of the neurons, with red the highest firing and green the lowest. SI, somatic sensory cortex; VPM, ventral posterior medial nucleus of the thalamus; SpV, spinal nucleus of the trigeminal brainstem complex; PrV, principal nucleus of the brainstem trigeminal complex. (From Nicholelis et al., 1997.)

Receptor density and receptive field sizes in different regions are not the only factors determining somatic sensation. Psychophysical analysis of tactile performance suggests that something more than the cutaneous periphery is needed to explain variations in tactile perception. For instance, sensory thresholds in two-point discrimination tests vary with practice, fatigue, and stress. The contextual significance of stimuli is also important in determining what we actually feel; even though we spend most of the day wearing clothes, we usually ignore the tactile stimulation that they produce. Some aspect of the mechanosensory system allows us to filter out this information and pay attention to it only when necessary. The fascinating phenomenon of "phantom limb" sensations after amputation (see Box C in Chapter 9) provides further evidence that tactile perception is not fully explained by the



(B) Receptive fields of two cortical neurons from two different animals. Each panel represents the matrix of whiskers on the animals' snout (whisker columns are on the *x* axis and whisker rows on the *y* axis) for a 4-ms epoch of poststimulus time. Within a particular time period, the center of the receptive field is defined as the whisker eliciting the greatest response magnitude (yellow). Note that the receptive field centers shift as a function of time. (From Ghazanfar and Nicholelis, 1998.)

vary as a function of time: The neuron responds differently to a spatially defined stimulus as the period of stimulation proceeds (see Figures A and B).

This coupling of space and time can also be demonstrated at level of somatotopic maps. By recording the activity of single neurons located in different regions of the map simultaneously, it is apparent that the stimulation of a small area of the skin tends to excite more and more neurons as time goes by. Thus, many more neurons than those located in the area of the map directly representing the stimulated skin actually respond to the stimulus, albeit at longer latencies.

The end result of these more complex neuronal responses is the emergence of spatiotemporal representations at all levels of the somatic sensory system. Thus, contrary to the classical notion of receptive fields, the somatic sensory system processes information in a dynamic way. Such processing is not only relevant for the normal operation of the system, but may also account for some aspects of adult plasticity (see Chapter 24).

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peripheral information that travels centrally. The central nervous system clearly plays an active role in determining the perception of the mechanical forces that act on us.

Mechanoreceptors Specialized for Proprioception

Whereas cutaneous mechanoreceptors provide information derived from external stimuli, another major class of receptors provides information about mechanical forces arising from the body itself, the musculoskeletal system in particular. These are called **proprioceptors**, roughly meaning "receptors for self." The purpose of proprioceptors is primarily to give detailed and continuous information about the position of the limbs and other body parts in space (specialized mechanoreceptors also exist in the heart and major vessels to provide information about blood pressure, but these neurons are considered to be part of the visceral motor system; see Chapter 20). Low-threshold mechanoreceptors, including muscle spindles, Golgi tendon organs, and joint receptors, provide this kind of sensory information, which is essential to the accurate performance of complex movements. Information about the position and motion of the head is particularly important; in this case, proprioceptors are integrated with the highly specialized vestibular system, which is considered separately in Chapter 13.

The most detailed knowledge about proprioception derives from studies of **muscle spindles**, which are found in all but a few striated (skeletal) muscles. Muscle spindles consist of four to eight specialized **intrafusal muscle fibers** surrounded by a capsule of connective tissue. The intrafusal fibers are distributed among the ordinary (extrafusal) fibers of skeletal muscle in a parallel arrangement (Figure 8.5). In the largest of the several intrafusal fibers, the nuclei are collected in an expanded region in the center of the fiber called a bag; hence the name *nuclear bag fibers*. The nuclei in the remaining two to six smaller intrafusal fibers are lined up single file, with the result that these fibers are called *nuclear chain fibers*. Myelinated sensory axons belonging to group Ia innervate muscle spindles by encircling the middle portion of both types of intrafusal fibers (see Figure 8.5 and Table 8.1). The Ia axon terminal is known as the **primary sensory ending** of the spindle. Secondary innervation is provided by group II axons that innervate the nuclear chain fibers and give off a minor branch to the nuclear bag fibers. The intrafusal muscle fibers contract when commanded to do so by motor axons derived from a pool of specialized motor neurons in the spinal cord (called **γ motor neurons**). The major function of muscle spindles is to provide information about muscle length (that is, the degree to which they are being stretched). A detailed account of how these important receptors function during movement is given in Chapters 15 and 16.

The density of spindles in human muscles varies. Large muscles that generate coarse movements have relatively few spindles; in contrast, extraocular muscles and the intrinsic muscles of the hand and neck are richly supplied with spindles, reflecting the importance of accurate eye movements, the need to manipulate objects with great finesse, and the continuous demand for precise positioning of the head. This relationship between receptor den-

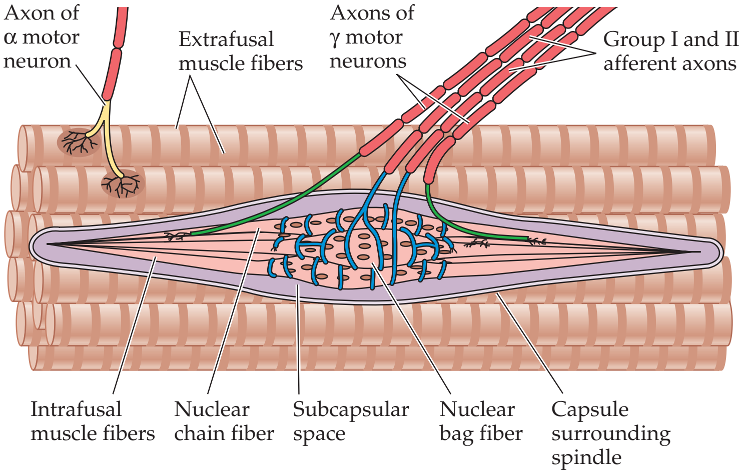


Figure 8.5 A muscle spindle and several extrafusal muscle fibers. See text for description. (After Matthews, 1964.)

sity and muscle size is consistent with the generalization that the sensory motor apparatus at all levels of the nervous system is much richer for the hands, head, speech organs, and other parts of the body that are used to perform especially important and demanding tasks. Spindles are lacking altogether in a few muscles, such as those of the middle ear, which do not require the kind of feedback that these receptors provide.

Whereas muscle spindles are specialized to signal changes in muscle *length*, low-threshold mechanoreceptors in tendons inform the central nervous system about changes in muscle *tension*. These mechanoreceptors, called **Golgi tendon organs**, are innervated by branches of group Ib afferents and are distributed among the collagen fibers that form the tendons (see Chapter 15).

Finally, rapidly adapting mechanoreceptors in and around joints gather dynamic information about limb position and joint movement. The function of these **joint receptors** is not well understood.

Active Tactile Exploration

Tactile discrimination—that is, perceiving the detailed shape or texture of an object—normally entails active exploration. In humans, this is typically accomplished by using the hands to grasp and manipulate objects, or by moving the fingers across a surface so that a sequence of contacts between the skin and the object of interest is established. Psychophysical evidence indicates that relative movement between the skin and a surface is the single most important requirement for accurate discrimination of texture. Animal experiments confirm the dependence of tactile discrimination on active exploration. Rats, for instance, discriminate the details of texture by rhythmically brushing their facial whiskers across surfaces. Active touching, which is called **haptics**, involves the interpretation of complex spatiotemporal patterns of stimuli that are likely to activate many classes of mechanoreceptors. Haptics also requires dynamic interactions between motor and sensory signals, which presumably induce sensory responses in central neurons that differ from the responses of the same cells during passive stimulation of the skin (see Box B).

The Major Afferent Pathway for Mechanosensory Information: The Dorsal Column–Medial Lemniscus System

The action potentials generated by tactile and other mechanosensory stimuli are transmitted to the spinal cord by afferent sensory axons traveling in the peripheral nerves. The neuronal cell bodies that give rise to these first-order axons are located in the **dorsal root** (or **sensory**) **ganglia** associated with each segmental spinal nerve (see Figure 8.1 and Box C). Dorsal root ganglion cells are also known as **first-order neurons** because they initiate the sensory process. The ganglion cells thus give rise to long peripheral axons that end in the somatic receptor specializations already described, and shorter central axons that reach the dorsolateral region of the spinal cord via the **dorsal** (**sensory**) **roots** of each spinal cord segment. The large myelinated fibers that innervate low-threshold mechanoreceptors are derived from the largest neurons in these ganglia, whereas the smaller ganglion cells give rise to smaller afferent nerve fibers that end in the high-threshold nociceptors and thermoceptors (see Table 8.1).

Depending on whether they belong to the mechanosensory system or to the pain and temperature system, the first-order axons carrying information from somatic receptors have different patterns of termination in the spinal cord and define distinct somatic sensory pathways within the central nervous system (see Figure 8.1). **The dorsal column–medial lemniscus pathway** carries the majority of information from the mechanoreceptors that mediate tactile discrimination and proprioception (Figure 8.6); the **spinothalamic** (**anterolateral**) **pathway** mediates pain and temperature sensation and is described in Chapter 9. This difference in the afferent pathways of these modalities is one of the reasons that pain and temperature sensation is treated separately here.

Upon entering the spinal cord, the first-order axons carrying information from peripheral mechanoreceptors bifurcate into ascending and descending branches, which in turn send collateral branches to several spinal segments. Some collateral branches penetrate the dorsal horn of the cord and synapse on neurons located mainly in a region called Rexed's laminae III–V. These synapses mediate, among other things, segmental reflexes such as the "knee-jerk" or myotatic reflex described in Chapter 1, and are further considered in Chapters 15 and 16. The major branch of the incoming axons, however, ascends ipsilaterally through the **dorsal columns** (also called the *posterior funiculi*) of the cord, all the way to the lower medulla, where it terminates by contacting **second-order neurons** in the **gracile** and **cuneate nuclei** (together referred to as the **dorsal column nuclei**; see Figures 8.1 and 8.6A). Axons in the dorsal columns are topographically organized such that the fibers that convey information from lower limbs are in the medial subdivision of the dorsal columns, called the **gracile tract**, a fact of some significance in the clinical localization of neural injury. The lateral subdivision, called the **cuneate tract**, contains axons conveying information from the upper limbs, trunk, and neck. At the level of the upper thorax, the dorsal columns account for more than a third of the cross-sectional area of the human spinal cord.

Despite their size, lesions limited to the dorsal columns of the spinal cord in both humans and monkeys have only a modest effect on the performance of simple tactile tasks. Such lesions, however, do impede the ability to detect the direction and speed of tactile stimuli, as well as degrading the ability to sense the position of the limbs in space. Dorsal column lesions may also reduce a patient's ability to initiate active movements related to tactile exploration. For instance, such individuals have difficulty recognizing numbers and letters drawn on their skin. The relatively mild deficit that follows dorsal column lesions is presumably explained by the fact that some axons responsible for cutaneous mechanoreception also run in the spinothalamic (pain and temperature) pathway, as described in Chapter 9.

The second-order relay neurons in the dorsal column nuclei send their axons to the somatic sensory portion of the thalamus (see Figure 8.6A). The axons from dorsal column nuclei project in the dorsal portion of each side of the lower brainstem, where they form the **internal arcuate tract**. The internal arcuate axons subsequently cross the midline to form another named tract that is elongated dorsoventrally, the **medial lemniscus**. (The crossing of these fibers is called the *decussation* of the medial lemniscus, from the roman numeral "X," or *decem*; the word *lemniscus* means "ribbon.")

In a cross-section through the medulla, such as the one shown in Figure 8.6A, the medial lemniscal axons carrying information from the lower limbs are located ventrally, whereas the axons related to the upper limbs are located dorsally (again, a fact of some clinical importance). As the medial lemniscus ascends through the pons and midbrain, it rotates 90° laterally, so that the upper body is eventually represented in the medial portion of the tract, and the lower body in the lateral portion. The axons of the medial lem-

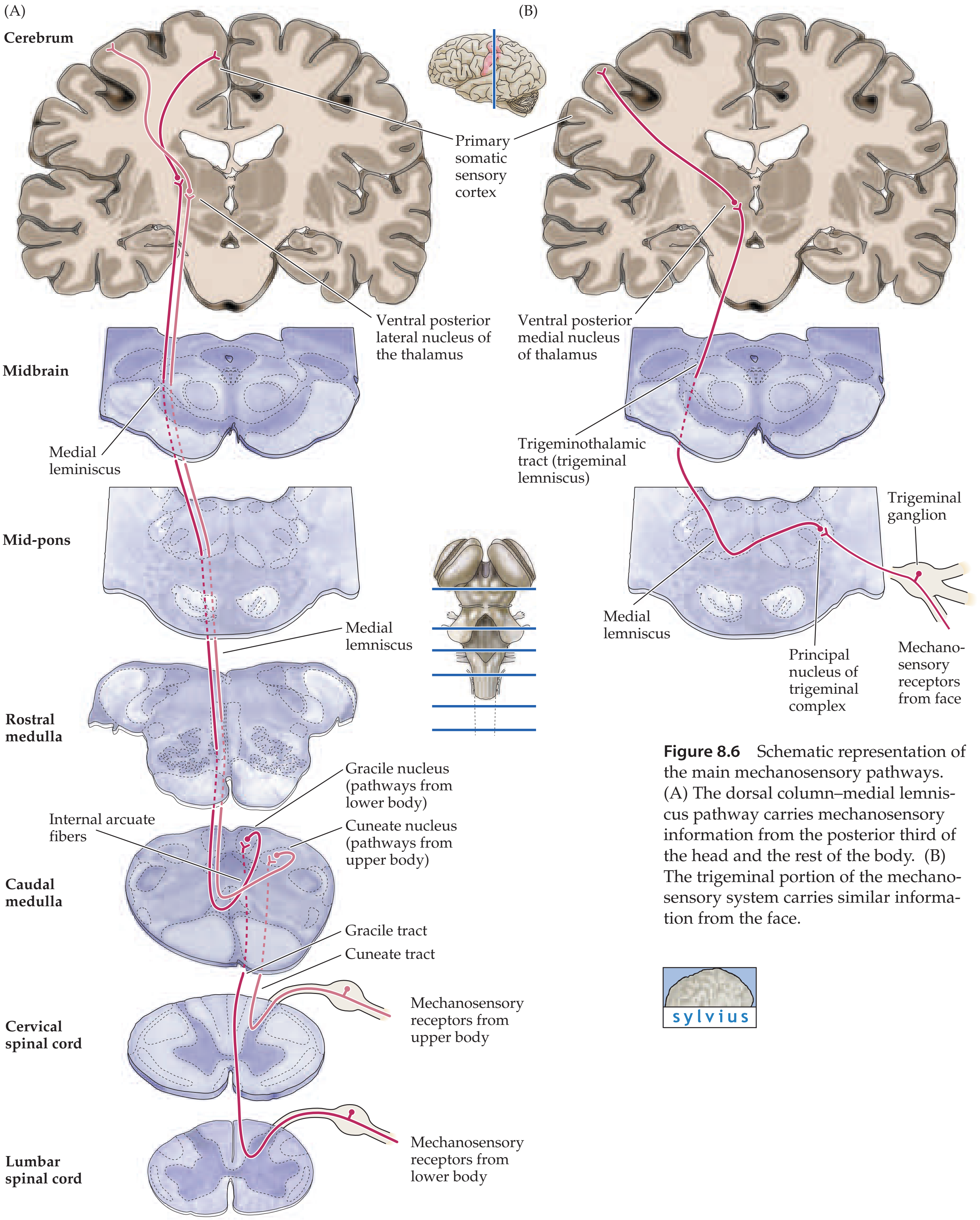
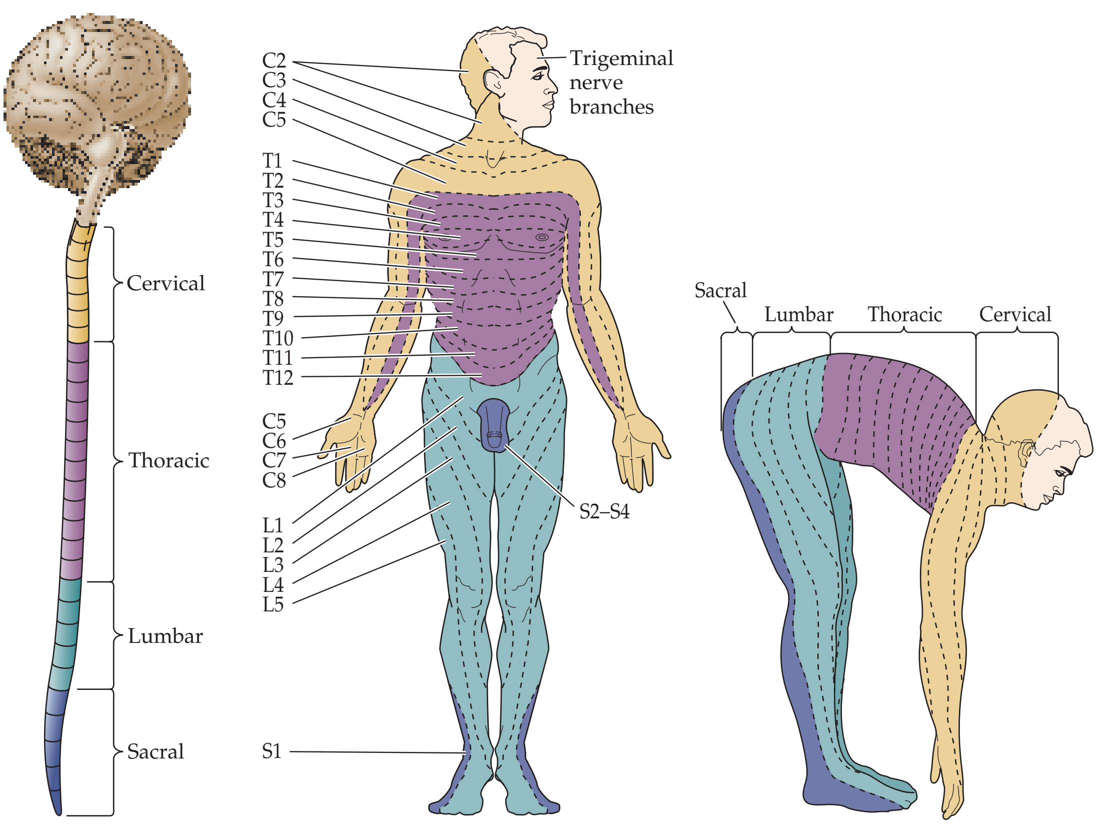

(A)
Cerebrum
Primary somatic sensory cortex
Ventral posterior lateral nucleus of the thalamus
Midbrain
Medial leminiscus
Mid-pons
Medial lemniscus
Rostral medulla
Internal arcuate fibers
Gracile nucleus (pathways from lower body)
Cuneate nucleus (pathways from upper body)
Caudal medulla
Gracile tract
Cuneate tract
Cervical spinal cord
Mechanosensory receptors from upper body
Lumbar spinal cord
Mechanosensory receptors from lower body
(B)
Ventral posterior medial nucleus of thalamus
Trigeminothalamic tract (trigeminal lemniscus)
Trigeminal ganglion
Medial lemniscus
Principal nucleus of trigeminal complex
Mechano-sensory receptors from face

Figure 8.6 Schematic representation of the main mechanosensory pathways. (A) The dorsal column–medial lemniscus pathway carries mechanosensory information from the posterior third of the head and the rest of the body. (B) The trigeminal portion of the mechanosensory system carries similar information from the face.

Box C

Dermatomes



The innervation arising from a single dorsal root ganglion and its spinal nerve is called a dermatome. The full set of sensory dermatomes is shown here for a typical adult. Knowledge of this arrangement is particularly important in defining the location of suspected spinal (and other) lesions. The numbers refer to the spinal segments by which each nerve is named. (After Rosenzweig et al., 2002.)

Each dorsal root (or sensory) ganglion and associated spinal nerve arises from an iterated series of embryonic tissue masses called somites. This fact of development explains the overall segmental arrangement of somatic nerves (and the targets they innervate) in the adult (see figure). The territory innervated by each spinal nerve is called a dermatome. In humans, the cutaneous area of each dermatome has been defined in patients in whom specific dorsal roots were affected (as in herpes zoster, or "shingles") or after surgical interruption (for relief of pain or other reasons). Such studies show that dermatomal maps vary among individuals. Moreover, dermatomes overlap substantially, so that injury to an individual dorsal root does not lead to complete loss of sensation in the relevant skin region, the overlap being more extensive for touch, pressure, and vibration than for pain and temperature. Thus, testing for pain sensation provides a more precise assessment of a segmental nerve injury than does testing for responses to touch, pressure, or vibration. Finally, the segmental distribution of proprioceptors does not follow the dermatomal map but is more closely allied with the pattern of muscle innervation. Despite these limitations, knowledge of dermatomes is essential in the clinical evaluation of neurological patients, particularly in determining the level of a spinal lesion.

niscus thus reach the ventral posterior lateral (VPL) nucleus of the thalamus, whose cells are the **third-order neurons** of the dorsal column–medial lemniscus system (see Figure 8.7).

The Trigeminal Portion of the Mechanosensory System

As noted, the dorsal column–medial lemniscus pathway described in the preceding section carries somatic information from only the upper and lower body and from the posterior third of the head. Tactile and proprioceptive information from the face is conveyed from the periphery to the thalamus by a different route. Information derived from the face is transmitted to the central nervous system via the **trigeminal somatic sensory system** (Figure 8.6B). Low-threshold mechanoreception in the face is mediated by first-order neurons in the trigeminal (cranial nerve V) ganglion. The peripheral processes of these neurons form the three main subdivisions of **the trigeminal nerve** (the **ophthalmic**, **maxillary**, and **mandibular branches**), each of which innervates a well-defined territory on the face and head, including the teeth and the mucosa of the oral and nasal cavities. The central processes of trigeminal ganglion cells form the sensory roots of the trigeminal nerve; they enter the brainstem at the level of the pons to terminate on neurons in the subdivisions of the **trigeminal brainstem complex**.

The trigeminal complex has two major components: the **principal nucleus** (responsible for processing mechanosensory stimuli), and the **spinal nucleus** (responsible for processing painful and thermal stimuli). Thus, most of the axons carrying information from low-threshold cutaneous mechanoreceptors in the face terminate in the principal nucleus. In effect, this nucleus corresponds to the dorsal column nuclei that relay mechanosensory information from the rest of the body. The spinal nucleus corresponds to a portion of the spinal cord that contains the second-order neurons in the pain and temperature system for the rest of the body (see Chapter 9). The second-order neurons of the trigeminal brainstem nuclei give off axons that cross the midline and ascend to the ventral posterior medial (VPM) nucleus of the thalamus by way of the **trigeminothalamic tract** (also called the trigeminal lemniscus).

The Somatic Sensory Components of the Thalamus

Each of the several ascending somatic sensory pathways originating in the spinal cord and brainstem converge on the thalamus (Figure 8.7). The **ventral posterior complex** of the thalamus, which comprises a lateral and a medial nucleus, is the main target of these ascending pathways. As already mentioned, the more laterally located **ventral posterior lateral (VPL) nucleus** receives projections from the medial lemniscus carrying all somatosensory information from the body and posterior head, whereas the more medially located **ventral posterior medial (VPM) nucleus** receives axons from the trigeminal lemniscus (that is, mechanosensory and nociceptive information from the face). Accordingly, the ventral posterior complex of the thalamus contains a complete representation of the somatic sensory periphery.

The Somatic Sensory Cortex

The axons arising from neurons in the ventral posterior complex of the thalamus project to cortical neurons located primarily in layer IV of the somatic sensory cortex (see Figure 8.7; also see Box A in Chapter 25 for a more detailed description of cortical lamination). The **primary somatic sensory cortex** in humans (also called **SI**), which is located in the postcentral gyrus of the parietal lobe, comprises four distinct regions, or fields, known as **Brodmann's areas 3a, 3b, 1**, and **2**. Experiments carried out in nonhuman primates indicate that neurons in areas 3b and 1 respond primarily to cutaneous stimuli, whereas neurons in 3a respond mainly to stimulation of proprioceptors; area 2 neurons process both tactile and proprioceptive stimuli. Mapping studies in humans and other primates show further that each

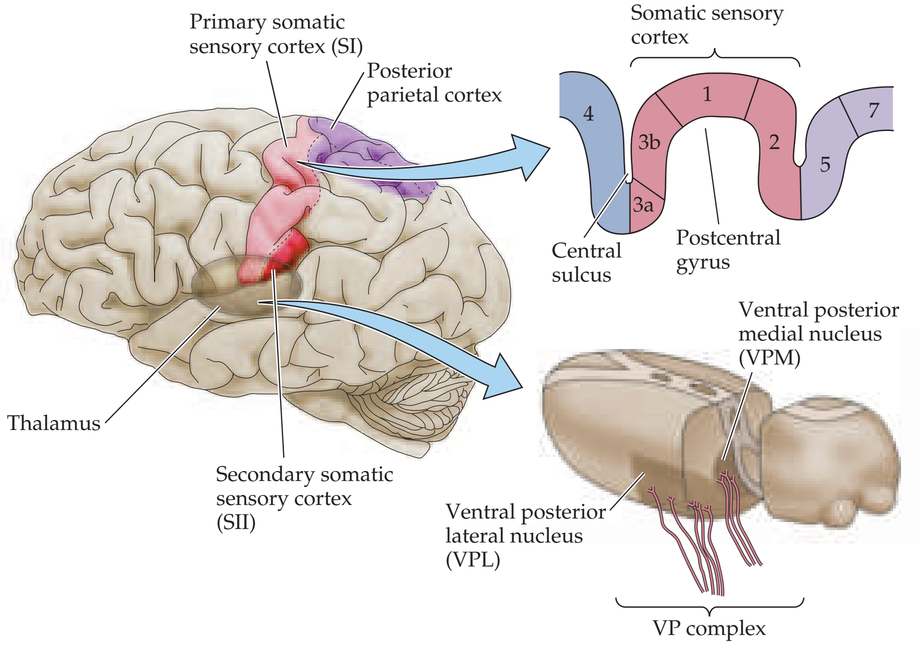

Primary somatic sensory cortex (SI)
Posterior parietal cortex
Somatic sensory cortex
4
1
7
3b
2
5
3a
Central sulcus
Postcentral gyrus
Ventral posterior medial nucleus (VPM)
Thalamus
Secondary somatic sensory cortex (SII)
Ventral posterior lateral nucleus (VPL)
VP complex

Figure 8.7 Diagram of the somatic sensory portions of the thalamus and their cortical targets in the postcentral gyrus. The ventral posterior nuclear complex comprises the VPM, which relays somatic sensory information carried by the trigeminal system from the face, and the VPL, which relays somatic sensory information from the rest of the body. Inset above shows organization of the primary somatosensory cortex in the postcentral gyrus, shown here in a section cutting across the gyrus from anterior to posterior. (After Brodal, 1992, and Jones et al., 1982.)

of these four cortical areas contains a separate and complete representation of the body. In these **somatotopic maps**, the foot, leg, trunk, forelimbs, and face are represented in a medial to lateral arrangement, as shown in Figures 8.8A,B and 8.9.

Although the topographic organization of the several somatic sensory areas is similar, the functional properties of the neurons in each region and their organization are distinct (Box D). For instance, the neuronal receptive fields are relatively simple in area 3b; the responses elicited in this region are generally to stimulation of a single finger. In areas 1 and 2, however, the majority of the receptive fields respond to stimulation of multiple fingers. Furthermore, neurons in area 1 respond preferentially to particular directions of skin stimulation, whereas many area 2 neurons require complex stimuli to activate them (such as a particular shape). Lesions restricted to area 3b produce a severe deficit in both texture and shape discrimination. In contrast, damage confined to area 1 affects the ability of monkeys to perform accurate texture discrimination. Area 2 lesions tend to produce deficits in finger coordination, and in shape and size discrimination.

A salient feature of cortical maps, recognized soon after their discovery, is their failure to represent the body in actual proportion. When neurosurgeons determined the representation of the human body in the primary sensory (and motor) cortex, the homunculus (literally, “little man”) defined by such mapping procedures had a grossly enlarged face and hands compared to the torso and proximal limbs (Figure 8.8C). These anomalies arise because

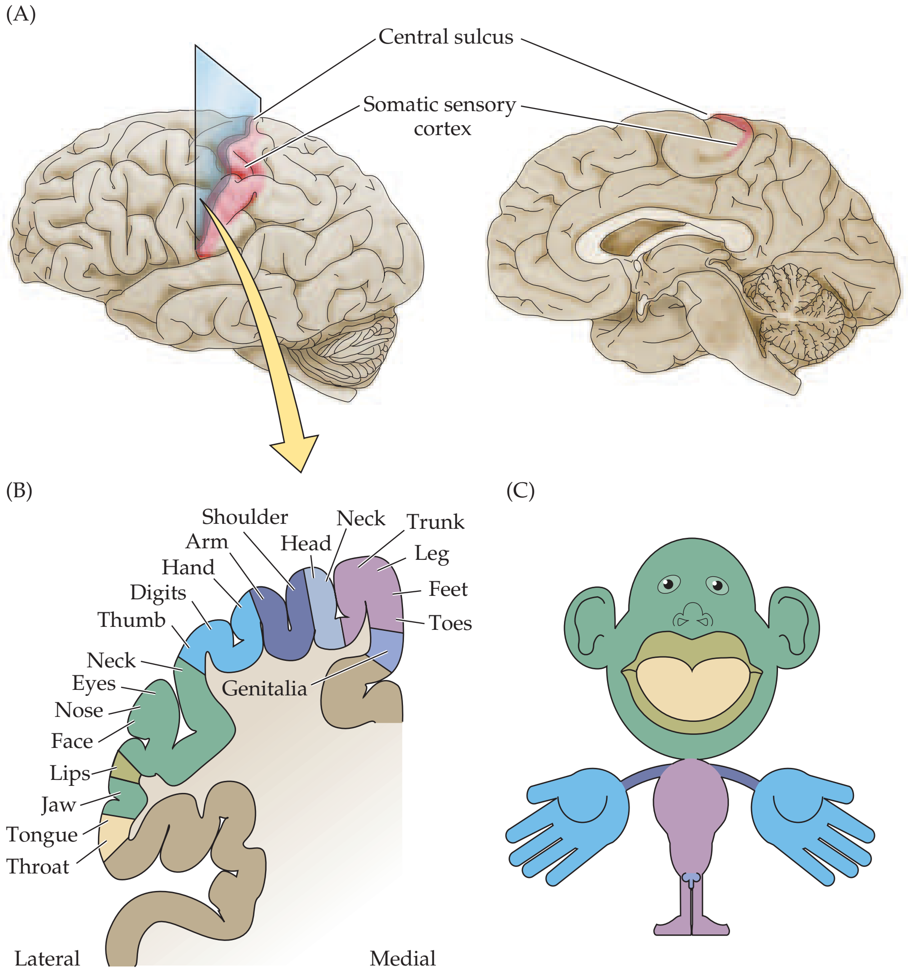


Figure 8.8 Somatotopic order in the human primary somatic sensory cortex. (A) Diagram showing the region of the human cortex from which electrical activity is recorded following mechanosensory stimulation of different parts of the body. The patients in the study were undergoing neurosurgical procedures for which such mapping was required. Although modern imaging methods are now refining these classical data, the human somatotopic map first defined in the 1930s has remained generally valid. (B) Diagram along the plane in (A) showing the somatotopic representation of body parts from medial to lateral. (C) Cartoon of the homunculus constructed on the basis of such mapping. Note that the amount of somatic sensory cortex devoted to the hands and face is much larger than the relative amount of body surface in these regions. A similar disproportion is apparent in the primary motor cortex, for much the same reasons (see Chapter 17). (After Penfield and Rasmussen, 1950, and Corsi, 1991.)

manipulation, facial expression, and speaking are extraordinarily important for humans, requiring more central (and peripheral) circuitry to govern them. Thus, in humans, the cervical spinal cord is enlarged to accommodate the extra circuitry related to the hand and upper limb, and as stated earlier, the density of receptors is greater in regions such as the hands and lips. Such distortions are also apparent when topographical maps are compared across species. In the rat brain, for example, an inordinate amount of the somatic sensory cortex is devoted to representing the large facial whiskers that pro-

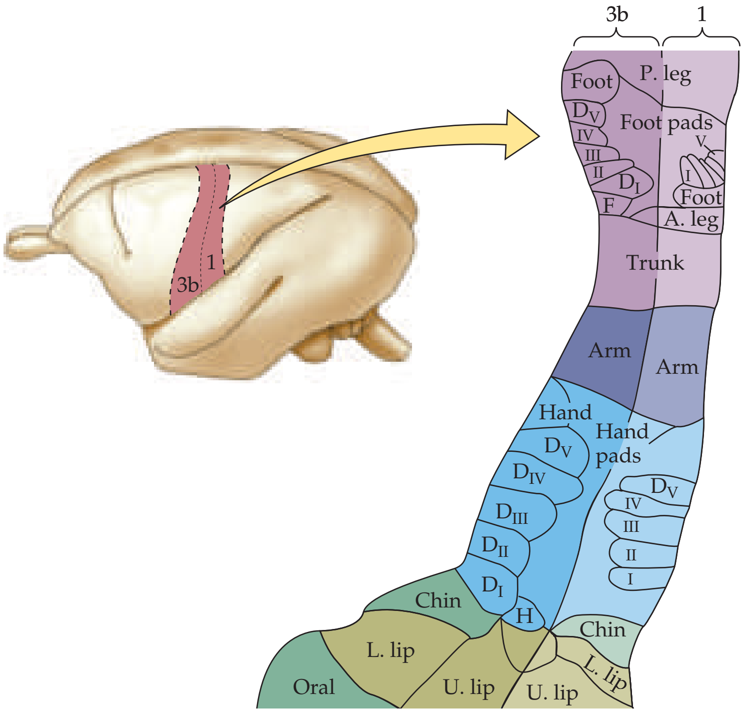


Figure 8.9 The primary somatic sensory map in the owl monkey based, as in Figure 8.8, on the electrical responsiveness of the cortex to peripheral stimulation. Much more detailed mapping is possible in experimental animals than in neurosurgical patients. The enlargement on the right shows areas 3b and 1, which process most cutaneous mechanosensory information. The arrangement is generally similar to that determined in humans. (After Kaas, 1983.)

vide a key component of the somatic sensory input for rats and mice (see Boxes B and D), while raccoons overrepresent their paws and the platypus its bill. In short, the sensory input (or motor output) that is particularly significant to a given species gets relatively more cortical representation.

Higher-Order Cortical Representations

Somatic sensory information is distributed from the primary somatic sensory cortex to "higher-order" cortical fields (as well as to subcortical structures). One of these higher-order cortical centers, the secondary somatosensory cortex (sometimes called SII and adjacent to the primary cortex; see Figure 8.7), receives convergent projections from the primary somatic sensory cortex and sends projections in turn to limbic structures such as the amygdala and hippocampus (see Chapters 28 and 30). This latter pathway is believed to play an important role in tactile learning and memory. Neurons in motor cortical areas in the frontal lobe also receive tactile information from the anterior parietal cortex and, in turn, provide feedback projections to several cortical somatic sensory regions. Such integration of sensory and motor information is considered in Chapters 19 and 25, where the role of these "association" regions of the cerebral cortex are discussed in more detail.

Finally, a fundamental but often neglected feature of the somatic sensory system is the presence of massive descending projections. These pathways originate in sensory cortical fields and run to the thalamus, brainstem, and spinal cord. Indeed, descending projections from the somatic sensory cortex outnumber ascending somatic sensory pathways! Although their physiological role is not well understood, it is generally assumed (with some experimental support) that descending projections modulate the ascending flow of sensory information at the level of the thalamus and brainstem.

Box D

Patterns of Organization within the Sensory Cortices: Brain Modules

Observations over the last 40 years have made it clear that there is an iterated substructure within the somatic sensory (and many other) cortical maps. This substructure takes the form of units called *modules*, each involving hundreds or thousands of nerve cells in repeating patterns. The advantages of these iterated patterns for brain function remain largely mysterious; for the neurobiologist, however, such iterated arrangements have provided important clues about cortical connectivity and the mechanisms by which neural activity influences brain development (see Chapters 22 and 23).

The observation that the somatic sensory cortex comprises elementary units of vertically linked cells was first noted in the 1920s by the Spanish neuroanatomist Rafael Lorente de Nó, based on his studies in the rat. The potential importance of cortical modularity remained largely unexplored until the 1950s, however, when electrophysiological experiments indicated an arrangement of repeating units in the brains of cats and, later, monkeys. Vernon Mountcastle, a neurophysiologist at Johns Hopkins, found that vertical microelectrode penetrations in the primary somatosensory cortex of these animals encountered cells that responded to the same sort of mechanical stimulus presented at the same location on the body surface. Soon after Mountcastle's pioneering work, David Hubel and Torsten Wiesel discovered a similar arrangement in the cat primary visual cortex. These and other observations led Mountcastle to the general view that "the elementary pattern of organization of the cerebral cortex is a vertically oriented column or cylinder of cells capable of input-output functions of considerable complexity." Since these discoveries in the late 1950s and early 1960s, the view that modular circuits represent a fundamental feature of the mammalian cerebral cortex has gained wide acceptance, and many such entities have now been described in various cortical regions (see figure).

This wealth of evidence for such patterned circuits has led many neuroscientists to conclude, like Mountcastle, that modules are a fundamental feature of the cerebral cortex, essential for perception, cognition, and perhaps even consciousness. Despite the prevalence of iterated modules, there are some problems with the view that modular units are universally important in cortical function. First, although modular circuits of a given class are readily seen in the brains of some species, they have not been found in the same brain regions of other, sometimes closely related, animals. Second, not all regions of the mammalian cortex are organized in a modular fashion. And third, no clear function of such modules has been discerned, much effort and speculation notwithstanding. This salient feature of the organization of the somatic sensory cortex and other cortical (and some subcortical) regions therefore remains a tantalizing puzzle.

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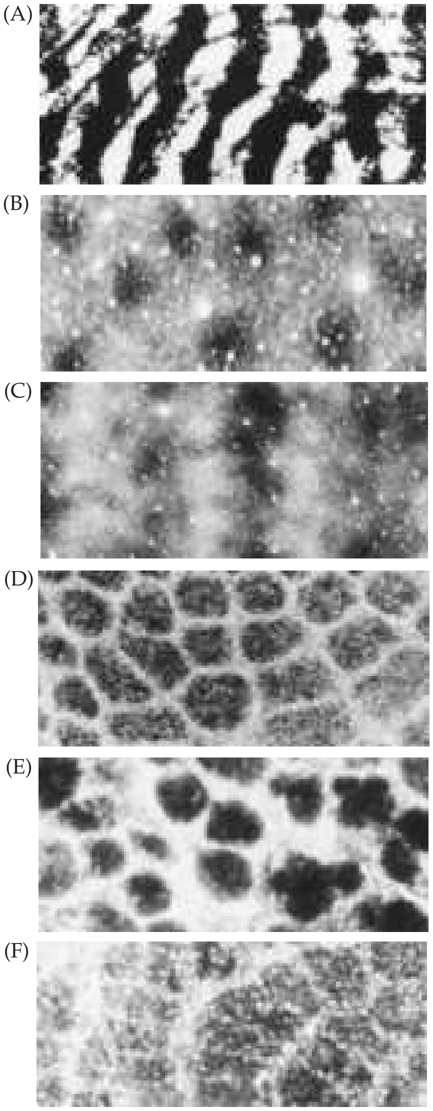

Examples of iterated, modular substructures in the mammalian brain. (A) Ocular dominance columns in layer IV in the primary visual cortex (V1) of a rhesus monkey. (B) Repeating units called "blobs" in layers II and III in V1 of a squirrel monkey. (C) Stripes in layers II and III in V2 of a squirrel monkey. (D) Barrels in layer IV in primary somatic sensory cortex of a rat. (E) Glomeruli in the olfactory bulb of a mouse. (F) Iterated units called "barreloids" in the thalamus of a rat. These and other examples indicate that modular organization is commonplace in the brain. These units are on the order of one hundred to several hundred microns across. (From Purves et al., 1992.)

Summary

The components of the somatic sensory system considered in this chapter process information conveyed by mechanical stimuli that impinge upon the body surface or that are generated within the body itself (proprioception). This processing is performed by neurons distributed across several brain structures that are connected by both ascending and descending pathways. Transmission of afferent mechanosensory information from the periphery to the brain begins with a variety of receptor types that initiate action potentials. This activity is conveyed centrally via a chain of neurons, referred to as the first-, second-, and third-order cells. First-order neurons are located in the dorsal root and cranial nerve ganglia. Second-order neurons are located in brainstem nuclei. Third-order neurons are found in the thalamus, from whence they project to the cerebral cortex. These pathways are topographically arranged throughout the system, the amount of cortical and subcortical space allocated to various body parts being proportional to the density of peripheral receptors. Studies of non-human primates show that specific cortical regions correspond to each functional submodality; area 3b, for example, processes information from low-threshold cutaneous receptors, and area 3a from proprioceptors. Thus, at least two broad criteria operate in the organization of the somatic sensory system: modality and somatotopy. The end result of this complex interaction is the unified perceptual representation of the body and its ongoing interaction with the environment.

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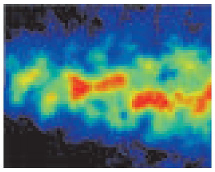
Chapter 9



Pain

Overview

A natural assumption is that the sensation of pain arises from excessive stimulation of the same receptors that generate other somatic sensations (i.e., those discussed in Chapter 8). This is not the case. Although similar in some ways to the sensory processing of ordinary mechanical stimulation, the perception of pain, called nociception, depends on specifically dedicated receptors and pathways. Since alerting the brain to the dangers implied by noxious stimuli differs substantially from informing it about innocuous somatic sensory stimuli, it makes good sense that a special subsystem be devoted to the perception of potentially threatening circumstances. The overriding importance of pain in clinical practice, as well as the many aspects of pain physiology and pharmacology that remain imperfectly understood, continue to make nociception an extremely active area of research.

Nociceptors

The relatively unspecialized nerve cell endings that initiate the sensation of pain are called **nociceptors** (*noci* is derived from the Latin *nocere*, "to hurt"). Like other cutaneous and subcutaneous receptors, they transduce a variety of stimuli into receptor potentials, which in turn trigger afferent action potentials (see Figure 8.2). Moreover, nociceptors, like other somatic sensory receptors, arise from cell bodies in dorsal root ganglia (or in the trigeminal ganglion) that send one axonal process to the periphery and the other into the spinal cord or brainstem (see Figure 8.1).

Because peripheral nociceptive axons terminate in unspecialized "free endings," it is conventional to categorize nociceptors according to the properties of the axons associated with them (see Table 8.1). As described in the previous chapter, the somatic sensory receptors responsible for the perception of innocuous mechanical stimuli are associated with myelinated axons that have relatively rapid conduction velocities. The axons associated with nociceptors, in contrast, conduct relatively slowly, being only lightly myelinated or, more commonly, unmyelinated. Accordingly, axons conveying information about pain fall into either the Aδ group of myelinated axons, which conduct at about 20 m/s, or into the C fiber group of unmyelinated axons, which conduct at velocities generally less than 2 m/s. Thus, even though the conduction of all nociceptive information is relatively slow, there are fast and slow pain pathways.

In general, the faster-conducting Aδ nociceptors respond either to dangerously intense mechanical or to mechanothermal stimuli, and have receptive fields that consist of clusters of sensitive spots. Other unmyelinated nociceptors tend to respond to thermal, mechanical, and chemical stimuli, and are

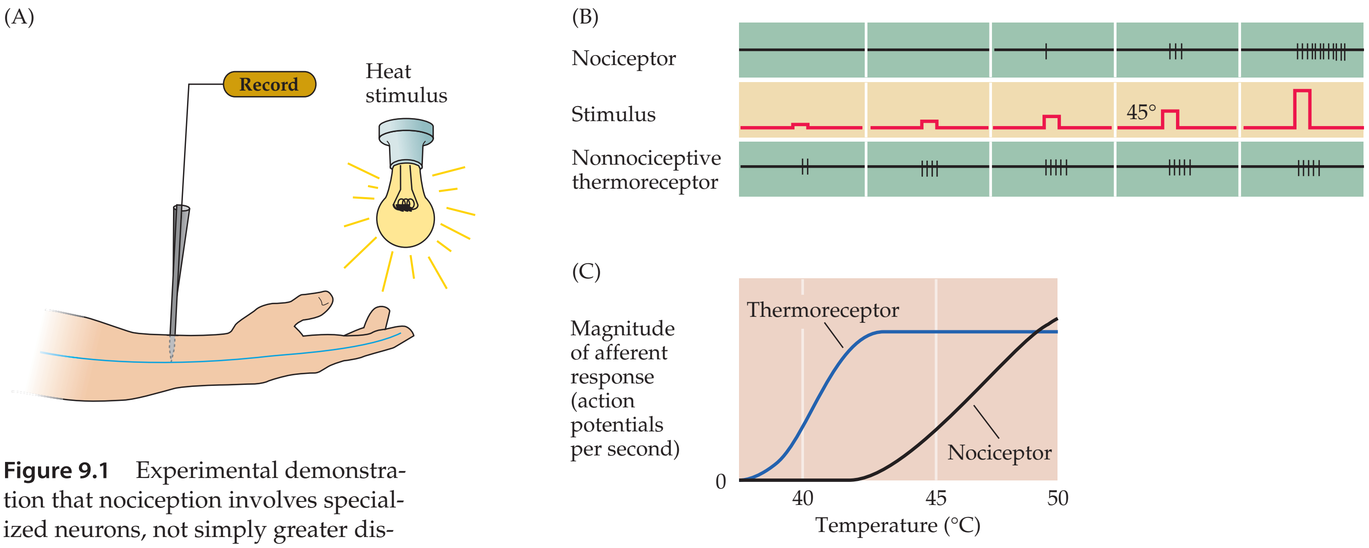


Figure 9.1 Experimental demonstration that nociception involves specialized neurons, not simply greater discharge of the neurons that respond to normal stimulus intensities. (A) Arrangement for transcutaneous nerve recording. (B) In the painful stimulus range, the axons of thermoreceptors fire action potentials at the same rate as at lower temperatures; the number and frequency of action potential discharge in the nociceptive axon, however, continues to increase. (Note that 45°C is the approximate threshold for pain.) (C) Summary of results. (After Fields, 1987.)

therefore said to be *polymodal*. In short, there are three major classes of nociceptors in the skin: **Aδ mechanosensitive nociceptors**; **Aδ mechanothermal nociceptors**; and **polymodal nociceptors**, the latter being specifically associated with C fibers. The receptive fields of all pain-sensitive neurons are relatively large, particularly at the level of the thalamus and cortex, presumably because the detection of pain is more important than its precise localization.

Studies carried out in both humans and experimental animals demonstrated some time ago that the rapidly conducting axons that subserve somatic sensory sensation are not involved in the transmission of pain. A typical experiment of this sort is illustrated in Figure 9.1. The peripheral axons responsive to nonpainful mechanical or thermal stimuli do not discharge at a greater rate when painful stimuli are delivered to the same region of the skin surface. The nociceptive axons, on the other hand, begin to discharge only when the strength of the stimulus (a thermal stimulus in the example in Figure 9.1) reaches high levels; at this same stimulus intensity, other thermoreceptors discharge at a rate no different from the maximum rate already achieved within the nonpainful temperature range, indicating that there are both nociceptive and nonnociceptive thermoreceptors. Equally important, direct stimulation of the large-diameter somatic sensory afferents at any frequency in humans does not produce sensations that are described as painful. In contrast, the smaller-diameter, more slowly conducting Aδ and C fibers are active when painful stimuli are delivered; and when stimulated electrically in human subjects, they produce pain.

How, then, do these different classes of nociceptors lead to the perception of pain? As mentioned, one way of determining the answer has been to stimulate different nociceptors in human volunteers while noting the sensations reported. In general, two categories of pain perception have been described: a sharp **first pain** and a more delayed, diffuse, and longer-lasting sensation that is generally called **second pain** (Figure 9.2A). Stimulation of the large, rapidly conducting Aα and Aβ axons in peripheral nerves does not elicit the sensation of pain. When the stimulus intensity is raised to a level that activates a subset of Aδ fibers, however, a tingling sensation or, if the stimulation is intense enough, a feeling of sharp pain is reported. If the stimulus intensity is increased still further, so that the small-diameter, slowly conducting C fiber axons are brought into play, then a duller, longer-lasting

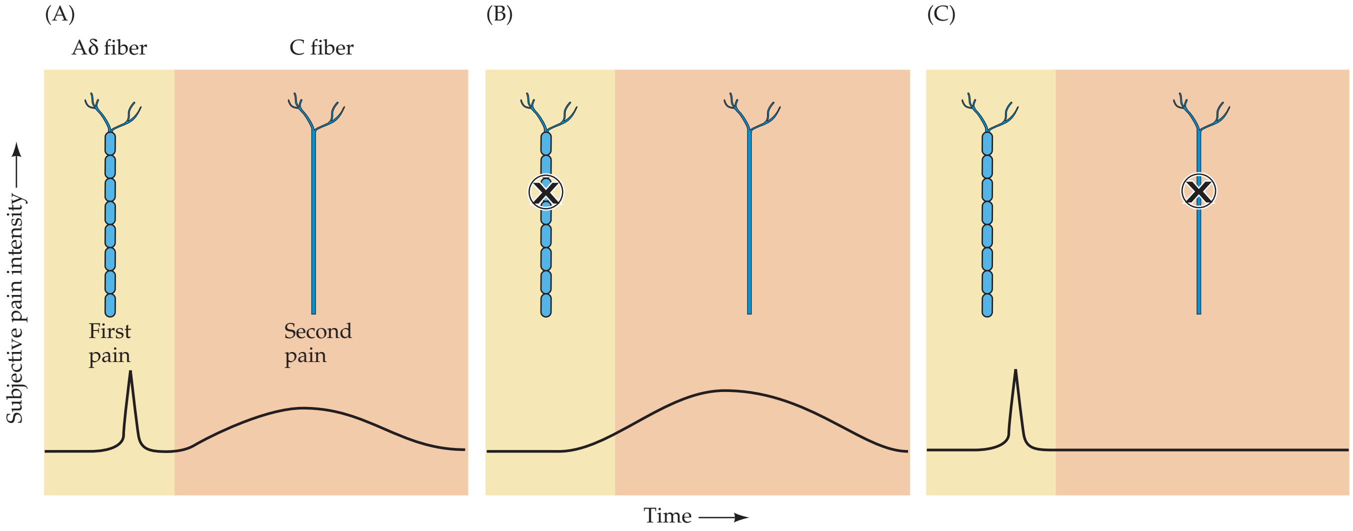


Figure 9.2 Pain can be separated into an early perception of sharp pain and a later sensation that is described as having a duller, burning quality. (A) First and second pain, as these sensations are called, are carried by different axons, as can be shown by (B) the selective blockade of the more rapidly conducting myelinated axons that carry the sensation of first pain, or (C) blockade of the more slowly conducting C fibers that carry the sensation of second pain. (After Fields, 1990.)

sensation of pain is experienced. It is also possible to selectively anesthetize C fibers and Aδ fibers; in general, these selective blocking experiments confirm that the Aδ fibers are responsible for first pain, and that C fibers are responsible for the duller, longer-lasting second pain (Figure 9.2B,C).

Transduction of Nociceptive Signals

Given the variety of stimuli (mechanical, thermal, and chemical) that can give rise to painful sensations, the transduction of nociceptive signals is a complex task. While many puzzles remain, some insights have come from the identification of specific receptors associated with nociceptive afferent endings. These receptors are sensitive to both heat and to capsaicin, the ingredient in chili peppers that is responsible for the familiar tingling or burning sensation produced by spicy foods (Box A). The so-called vanilloid receptor (VR-1 or TRPV1) is found in C and Aδ fibers and is activated by moderate heat (45°C—a temperature that is perceived as uncomfortable) as well as by capsaicin. Another type of receptor (vanilloid-like receptor, VRL-1 or TRPV2) has a higher threshold response to heat (52°C), is not sensitive to capsaicin, and is found in Aδ fibers. Both are members of the larger family of *transient receptor potential* (TRP) channels, first identified in studies of the phototransduction pathway in fruit flies and now known to comprise a large number of receptors sensitive to different ranges of heat and cold. Structurally, TRP channels resemble voltage-gated potassium or cyclic nucleotide-gated channels, having six transmembrane domains with a pore between domains 5 and 6. Under resting conditions the pore of the channel is closed. In the open, activated state, these receptors allow an influx of sodium and calcium that initiates the generation of action potentials in the nociceptive fibers.

Since the same receptor is responsive to heat as well as capsaicin, it is not surprising that chili peppers seem “hot.” A puzzle, however, is why the nervous system has evolved receptors that are sensitive to a chemical in chili peppers. As with the case of other plant compounds that selectively activate neural receptors (see the discussion of opiates below), it seems likely that TRPV1 receptors detect endogenous substances whose chemical structure resembles that of capsaicin. In fact, there is now some evidence that ‘endovanilloids’ that are produced by peripheral tissues in response to injury,

Box A

Capsaicin

Capsaicin, the principle ingredient responsible for the pungency of hot peppers, is eaten daily by over a third of the world's population. Capsaicin activates responses in a subset of nociceptive C fibers (polymodal nociceptors; see Chapter 9) by opening ligand-gated ion channels that permit the entry of Na^+ and Ca^{2+}. One of these channels (VR-1) has been cloned and has been found to be activated by capsaicin, acid, and anandamide (an endogeneous compound that also activates cannabanoid receptors), and by heating the tissue to about 43°C. It follows that anandamide and temperature are probably the endogenous activators of these channels. Mice whose VR-1 receptors have been knocked out drink capsaicin solutions as if they were water. Receptors for capsaicin have been found in polymodal nociceptors of all mammals, but are not present in birds (leading to the production of squirrel-proof birdseed laced with capsaicin!).

When applied to the mucus membranes of the oral cavity, capsaicin acts as an irritant, producing protective reactions. When injected into skin, it produces a burning pain and elicits hyperalgesia to thermal and mechanical stimuli. Repeated applications of capsaicin also desensitize pain fibers and prevent neuromodulators such as substance P, VIP, and somatostatin from being released by peripheral and central nerve terminals. Consequently, capsaicin is used clinically as an analgesic and anti-inflammatory agent; it is usually applied topically in a cream (0.075%) to relieve the pain associated with arthritis, postherpetic neuralgia, mastectomy, and trigeminal neuralgia. Thus, this remarkable chemical irritant not only gives gustatory pleasure on an enormous scale, but is also a useful pain reliever!

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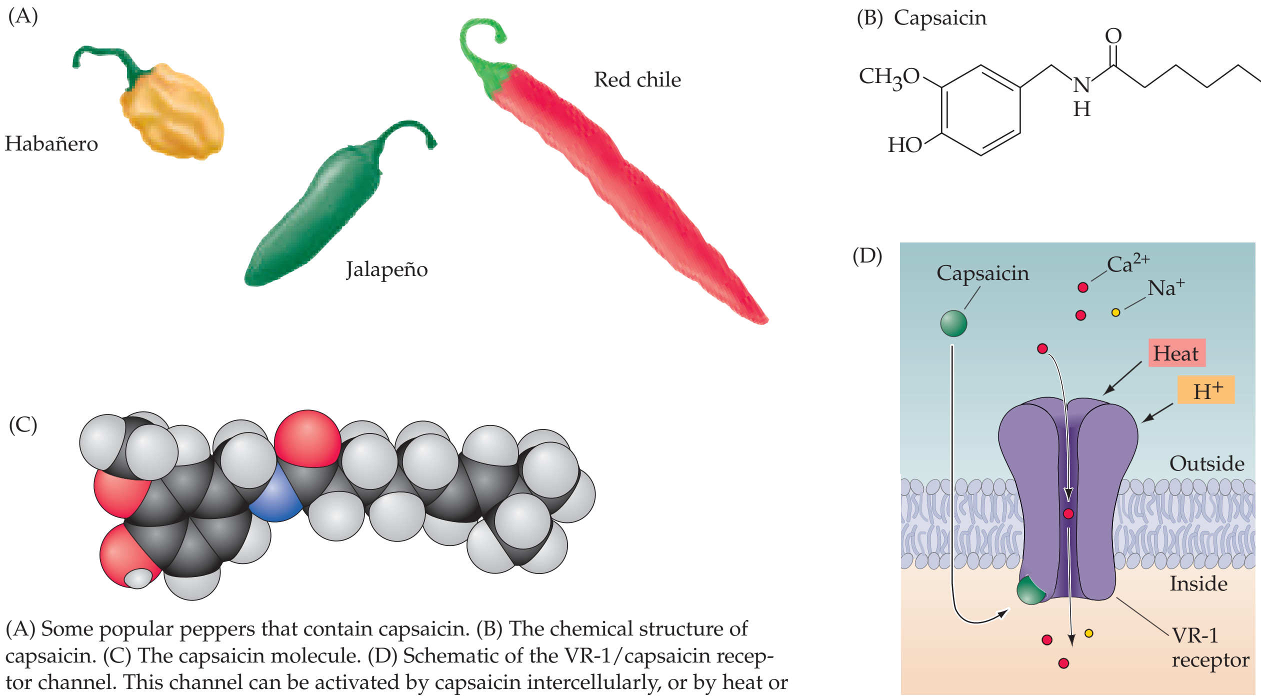


(A) Some popular peppers that contain capsaicin. (B) The chemical structure of capsaicin. (C) The capsaicin molecule. (D) Schematic of the VR-1/capsaicin receptor channel. This channel can be activated by capsaicin intercellularly, or by heat or protons (H^+) at the cell surface.

and that these substances, along with other factors, contribute to the nocieceptive response to injury.

Central Pain Pathways

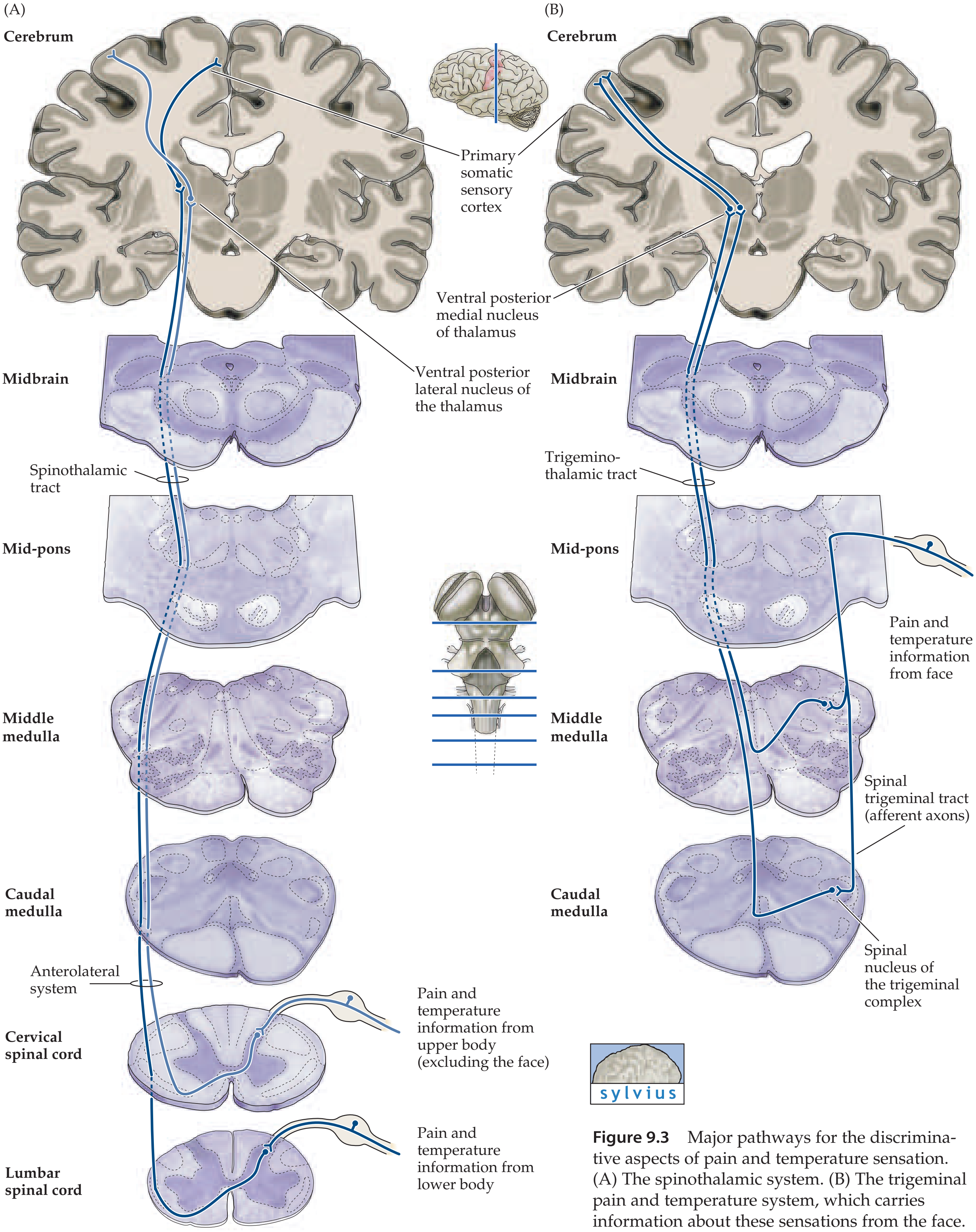
The pathways that carry information about noxious stimuli to the brain, as might be expected for such an important and multifaceted system, are also complex (see Boxes B and C). It helps in understanding this complexity to distinguish two components of pain: the sensory discriminative component, which signals the location, intensity, and quality of the noxious stimululation, and the affective-motivational component of pain—which signals the unpleasant quality of the experience, and enables the autonomic activation that follows a noxious stimulus (the classic fight-or-flight reaction; see Chapter 20). The discriminative component is thought to depend on pathways that target the traditional somatosensory areas of cortex, while the affective- motivational component is thought to depend on additional cortical and brainstem pathways. The major pathways are summarized in Figure 9.3.

Pathways responsible for the discriminative component of pain originate with other sensory neurons, in dorsal root ganglia and, like other sensory nerve cells the central axons of nociceptive nerve cells enter the spinal cord via the dorsal roots (Figure 9.3A). When these centrally projecting axons reach the dorsal horn of the spinal cord, they branch into ascending and descending collaterals, forming the **dorsolateral tract of Lissauer** (named after the German neurologist who first described this pathway in the late nineteenth century). Axons in Lissauer's tract typically run up and down for one or two spinal cord segments before they penetrate the gray matter of the dorsal horn. Once within the dorsal horn, the axons give off branches that contact neurons located in several of Rexed's laminae (these laminae are the descriptive divisions of the spinal gray matter in cross section, again named after the neuroanatomist who described these details in the 1950s).

The axons of these second-order neurons in the dorsal horn of the spinal cord cross the midline and ascend all the way to the brainstem and thalamus in the anterolateral (also called ventrolateral) quadrant of the contralateral half of the spinal cord. These fibers form the **spinothalamic tract**, the major ascending pathway for information about pain and temperature. This overall pathway is also referred to as the **anterolateral system**, much as the mechanosensory pathway is referred to as the dorsal column–medial lemniscus system.

The location of the spinothalamic tract is particularly important clinically because of the characteristic sensory deficits that follow certain spinal cord injuries. Since the mechanosensory pathway ascends ipsilaterally in the cord, a unilateral spinal lesion will produce sensory loss of touch, pressure, vibration, and proprioception below the lesion on the same side. The pathways for pain and temperature, however, cross the midline to ascend on the opposite side of the cord. Therefore, diminished sensation of pain below the lesion will be observed on the side *opposite* the mechanosensory loss (and the lesion). This pattern is referred to as a **dissociated sensory loss** and (together with local dermatomal signs; see Box C in Chapter 8) helps define the level of the lesion (Figure 9.4).

As is the case of the mechanosensory pathway, information about noxious and thermal stimulation of the face follows a separate route to the thalamus (see Figure 9.3B). First-order axons originating from the trigeminal ganglion cells and from ganglia associated with nerves VII, IX, and X carry information from facial nociceptors and thermoreceptors into the brainstem. After


(A)
Cerebrum
Primary somatic sensory cortex
Ventral posterior lateral nucleus of the thalamus
Midbrain
Spinothalamic tract
Mid-pons
Middle medulla
Caudal medulla
Anterolateral system
Cervical spinal cord
Pain and temperature information from upper body (excluding the face)
Lumbar spinal cord
Pain and temperature information from lower body
(B)
Cerebrum
Ventral posterior medial nucleus of thalamus
Midbrain
Trigemino-thalamic tract
Mid-pons
Pain and temperature information from face
Middle medulla
Spinal trigeminal tract (afferent axons)
Caudal medulla
Spinal nucleus of the trigeminal complex

sylvius

Figure 9.3 Major pathways for the discriminative aspects of pain and temperature sensation. (A) The spinothalamic system. (B) The trigeminal pain and temperature system, which carries information about these sensations from the face.

Box B

Referred Pain

Surprisingly, there are few, if any, neurons in the dorsal horn of the spinal cord that are specialized solely for the transmission of *visceral* pain. Obviously, we recognize such pain, but it is conveyed centrally via dorsal horn neurons that are also concerned with *cutaneous* pain. As a result of this economical arrangement, the disorder of an internal organ is sometimes perceived as cutaneous pain. A patient may therefore present to the physician with the complaint of pain at a site other than its actual source, a potentially confusing phenomenon called referred pain. The most common clinical example is anginal pain (pain arising from heart muscle that is not being adequately perfused with blood) referred to the upper chest wall, with radiation into the left arm and hand. Other important examples are gallbladder pain referred to the scapular region, esophageal pain referred to the chest wall, ureteral pain (e.g., from passing a kidney stone) referred to the lower abdominal wall, bladder pain referred to the perineum, and the pain from an inflamed appendix referred to the anterior abdominal wall around the umbilicus. Understanding referred pain can lead to an astute diagnosis that might otherwise be missed.

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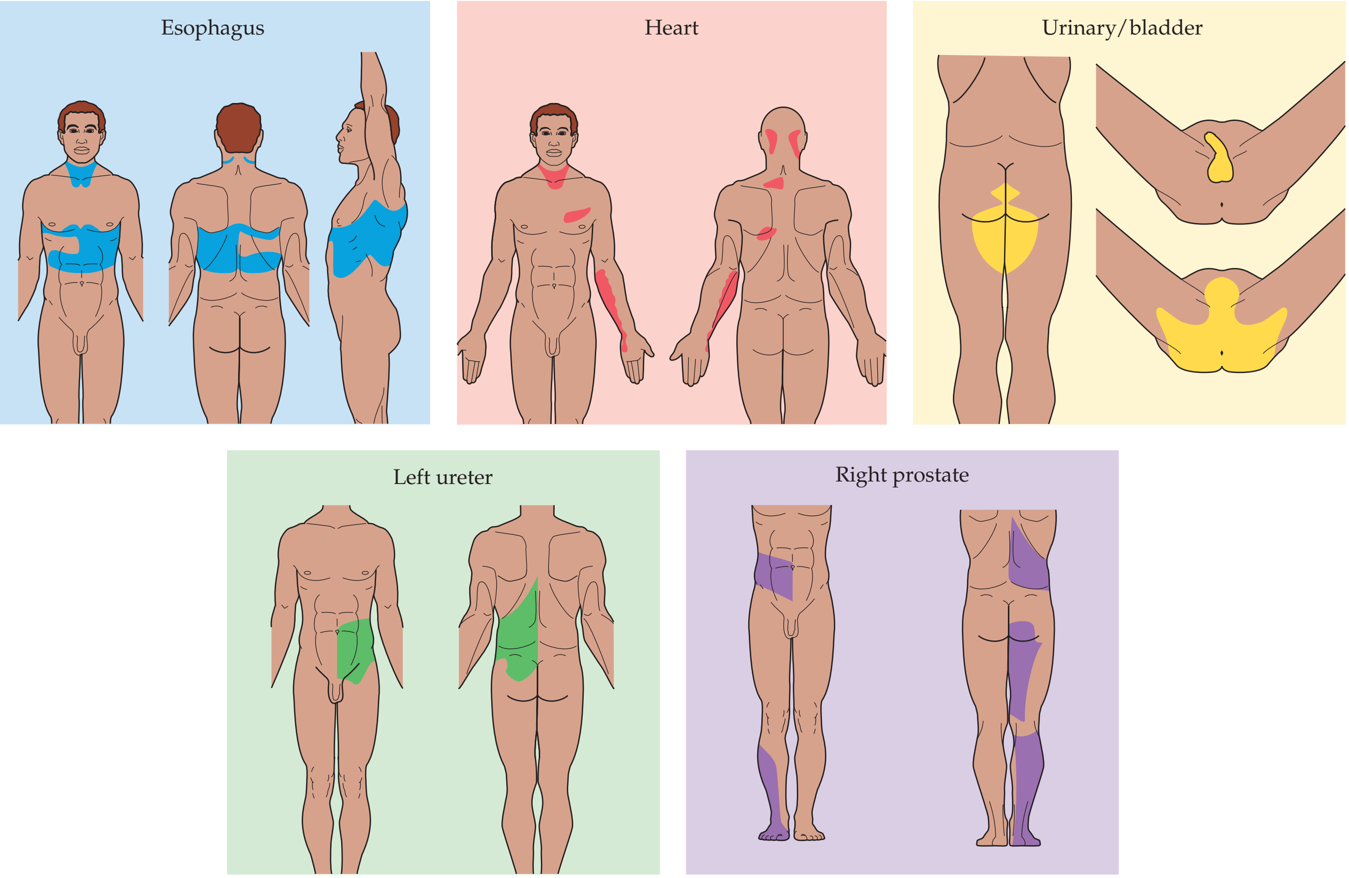
Examples of pain arising from a visceral disorder referred to a cutaneous region (color).



entering the pons, these small myelinated and unmyelinated trigeminal fibers *descend* to the medulla, forming the **spinal trigeminal tract** (or spinal tract of cranial nerve V), and terminate in two subdivisions of the spinal trigeminal complex: the pars interpolaris and pars caudalis. Axons from the second-order neurons in these two trigeminal nuclei, like their counterparts in the spinal cord, cross the midline and ascend to the contralateral thalamus in the **trigeminothalamic tract**.

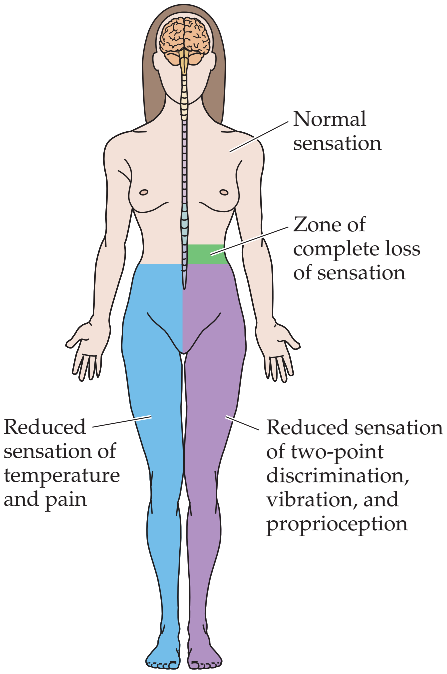

Normal sensation
Zone of complete loss of sensation
Reduced sensation of temperature and pain
Reduced sensation of two-point discrimination, vibration, and proprioception

Figure 9.4 Pattern of "dissociated" sensory loss following a spinal cord hemisection at the 10th thoracic level on the left side. This pattern, together with motor weakness on the same side as the lesion, is sometimes referred to as Brown-Séquard syndrome.

The principal target of the spinothalamic and trigeminothalamic pathway is the ventral posterior nucleus of the thalamus. Similar to the organization of the mechanosensory pathways, information from the body terminates in the VPL, while information from the face terminate in the VPM. These nuclei send their axons to primary and secondary somatosensory cortex. The nociceptive information transmitted to these cortical areas is thought to be responsible for the discriminative component of pain: identifying the location, the intensity, and quality of the stimulation. Consistent with this interpretation, electrophysiological recordings from nociceptive neurons in S1, show that these neurons have small localized receptive fields, properties commensurate with behavioral measures of pain localization.

The affective–motivational aspect of pain is evidently mediated by separate projections of the anterolateral system to the reticular formation of the midbrain (in particular the parabrachial nucleus), and to thalamic nuclei that lie medial to the ventral posterior nucleus (including the so-called intralaminar nuclei; see Figure 9.5). Studies in rodents show that neurons in the parabrachial nucleus respond to most types of noxious stimuli, and have large receptive fields that can include the whole surface of the body. Neurons in the parabrachial nucleus project in turn to the hypothalamus and the amygdala, thus providing nociceptive information to circuits known to be concerned with motivation and affect (see Chapter 28). These parabrachial targets are also the source of projections to the periaqueductal grey of the midbrain, a structure that plays an important role in the descending control of activity in the pain pathway. Nociceptive inputs to the parabrachial nucleus and to the ventral posterior nucleus arise from separate populations of neurons in the dorsal horn of the spinal cord. Parabrachial inputs arise from neurons in the most superficial part of the dorsal horn (lamina I), while ventral posterior inputs arise from deeper parts of the dorsal horn (e.g., lamina V). By taking advantage of the unique molecular signature of these two sets of neurons, it has been possible to selectively eliminate the nociceptive inputs to the parabrachial nucleus in rodents. In these animals, the behavioral responses to the presentation of noxious stimulation (capsaicin, for example) are substantially attenuated.

Projections from the anterolateral system to the medial thalamic nuclei provide nociceptive signals to areas in the frontal lobe, the insula and the cingulate cortex (Figure 9.5). In accord with this anatomy, functional imaging studies in humans have shown a strong correlation between activity in the anterior cingulate cortex and the experience of a painful stimulus. Moreover, experiments using hypnosis have been able to tease apart the neural response to changes in the intensity of a painful stimulus from changes in its unpleasantness. Changes in intensity are accompanied by changes in the activity of neurons in somatosensory cortex, with little change in the activity of cingulate cortex, whereas changes in unpleasantness are correlated with changes in the activity of neurons in cingulate cortex.

From this description, it should be evident that the full experience of pain involves the cooperative action of an extensive network of brain regions whose properties are only beginning to be understood (Box C). The cortical

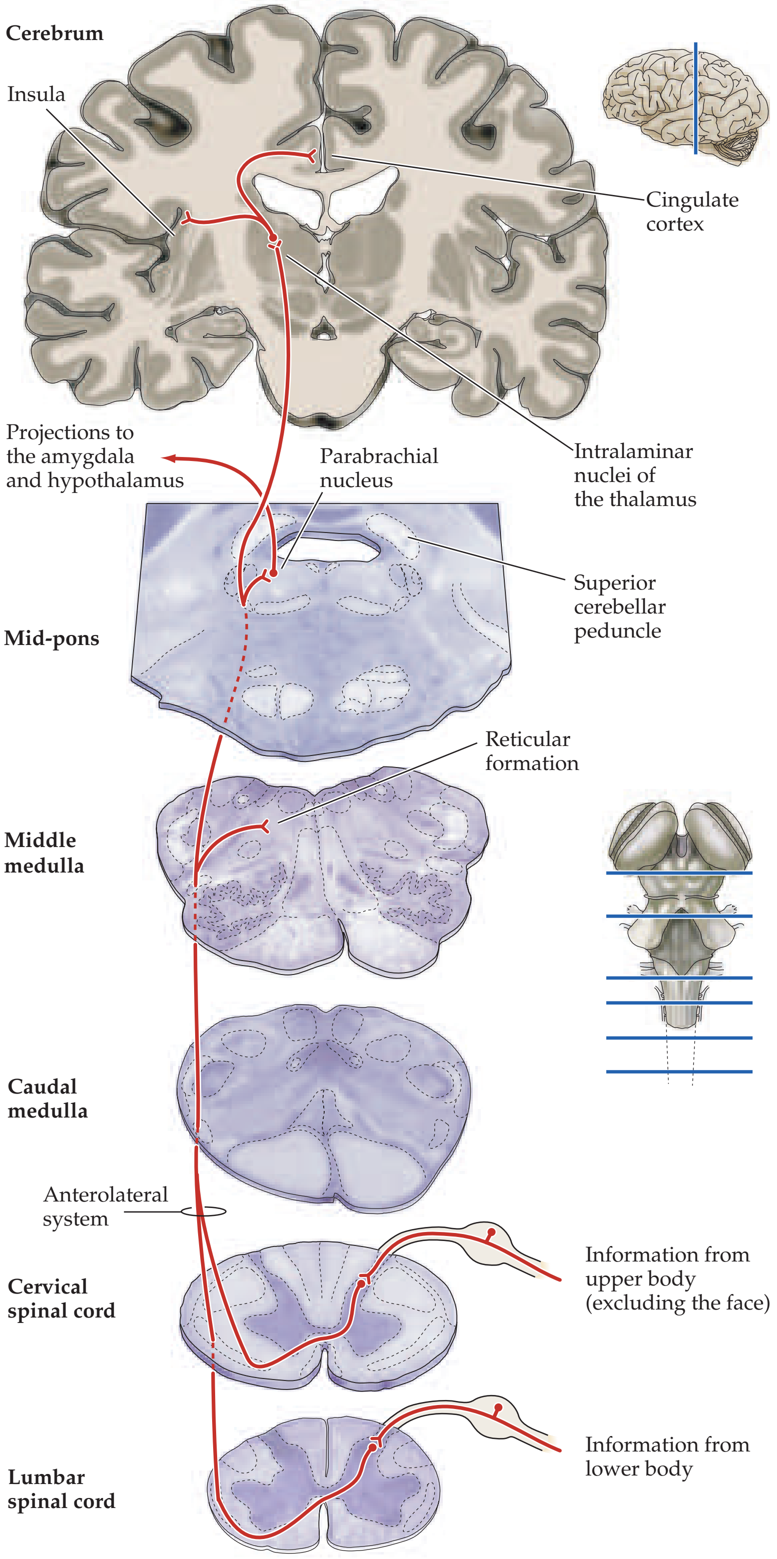

Cerebrum
Insula
Cingulate cortex
Projections to the amygdala and hypothalamus
Parabrachial nucleus
Intralaminar nuclei of the thalamus
Superior cerebellar peduncle
Mid-pons
Reticular formation
Middle medulla
Caudal medulla
Anterolateral system
Information from upper body (excluding the face)
Cervical spinal cord
Information from lower body
Lumbar spinal cord

Figure 9.5 Affective–motivational pain pathways. Nociceptive information critical for signaling the unpleasant quality of pain is mediated by projections to the reticular formation (including the parabrachial nucleus) and to the intralaminar nuclei of the thalamus.

Box C

A Dorsal Column Pathway for Visceral Pain

Chapters 8 and 9 present a framework for considering the central neural pathways that convey innocuous mechanosensory signals and painful signals from cutaneous and deep somatic sources. Considering just the signals derived from the body below the head, discriminitive mechanosensory and proprioceptive information travels to the ventral posterior thalamus via the dorsal-column medial lemniscal system (see Figure 8.6A), while nociceptive information travels to the same (and additional) thalamic relays via the anterolateral systems (see Figure 9.3A). But how do painful signals that arise in the visceral organs of the pelvis, abdomen, and thorax enter the central nervous system and ultimately reach consciousness?

The answer is via a newly discovered component of the dorsal column medial lemniscal pathway that conveys visceral nociception. Although Chapter 20 will present more information on the systems that receive and process visceral sensory information, at this juncture it is worth considering this component of the pain pathways and how this particular pathway has begun to impact clinical medicine.

Primary visceral afferents from the pelvic and abdominal viscera enter the spinal cord and synapse on second-order neurons in the dorsal horn of the lumbar-sacral spinal cord. As discussed in Box A and Chapter 20, some of these second-order neurons are cells that give rise to the anterolateral systems and contribute to referred visceral pain patterns. However, other neurons—perhaps primarily those that give rise to nociceptive signals—synapse upon neurons in the intermediate gray region of the spinal cord near the central canal. These neurons, in turn, send their axons not through the anterolateral white matter of the spinal cord (as might be expected for a pain pathway) but through the dorsal columns in a position very near the midline (see Figure A). Similarly, second-order neurons in the thoracic spinal cord that convey nociceptive signals from thoracic viscera send their axons rostrally through the dorsal columns along the dorsal intermediate septum, near the division of the gracile and cuneate fasciculi. These second order axons then synapse in the dorsal column nuclei of the caudal medulla, where neurons give rise to arcuate fibers that form the contralateral medial lemniscus and eventually synapse on thalamocortical projection neurons in the ventral-posterior thalamus.

This dorsal column visceral sensory projection now appears to be the principal pathway by which painful sensations arising in the viscera are detected and discriminated. Several observations support this conclusion: (1) neurons in the ventral posterior lateral nucleus, nucleus gracilis and near the central canal of the spinal cord all respond to noxious visceral stimulation; (2) responses of neurons in the ventral posterior lateral nucleus and nucleus gracilis to such stimulation are greatly reduced by spinal lesions of the dorsal columns (see Figure B), but not lesions of the anterolateral white matter; and (3) infusion of drugs that block nociceptive synaptic transmission into the intermediate gray region of the sacral spinal cord blocks the responses of neurons in the nucleus gracilis to noxious visceral stimulation, but not to innocuous cutaneous stimulation.

The discovery of this visceral sensory component in the dorsal-column medial lemniscal system has helped to explain why surgical transection of the axons that run in the medial part of the dorsal columns (a procedure termed *midline myelotomy*) generates significant relief from the debilitating pain that can result from visceral cancers in the abdomen and pelvis. Although the initial development of this surgical procedure preceded the elucidation of this visceral pain pathway, these new discoveries have renewed interest in midline myelotomy as a palliative neurosurgical intervention for cancer patients whose pain is otherwise unmanageable. Indeed, precise knowledge of the visceral sensory pathway in the dorsal columns has led to further refinements that permit a minimally invasive (“punctate”) surgical procedure that attempts to interupt the second-order axons of this pathway within just a single spinal segment (typically, a mid- or lower-thoracic level; see Figure C). In so doing, this procedure offers some hope to patients who struggle to maintain a reasonable quality of life in extraordinarily difficult circumstances.

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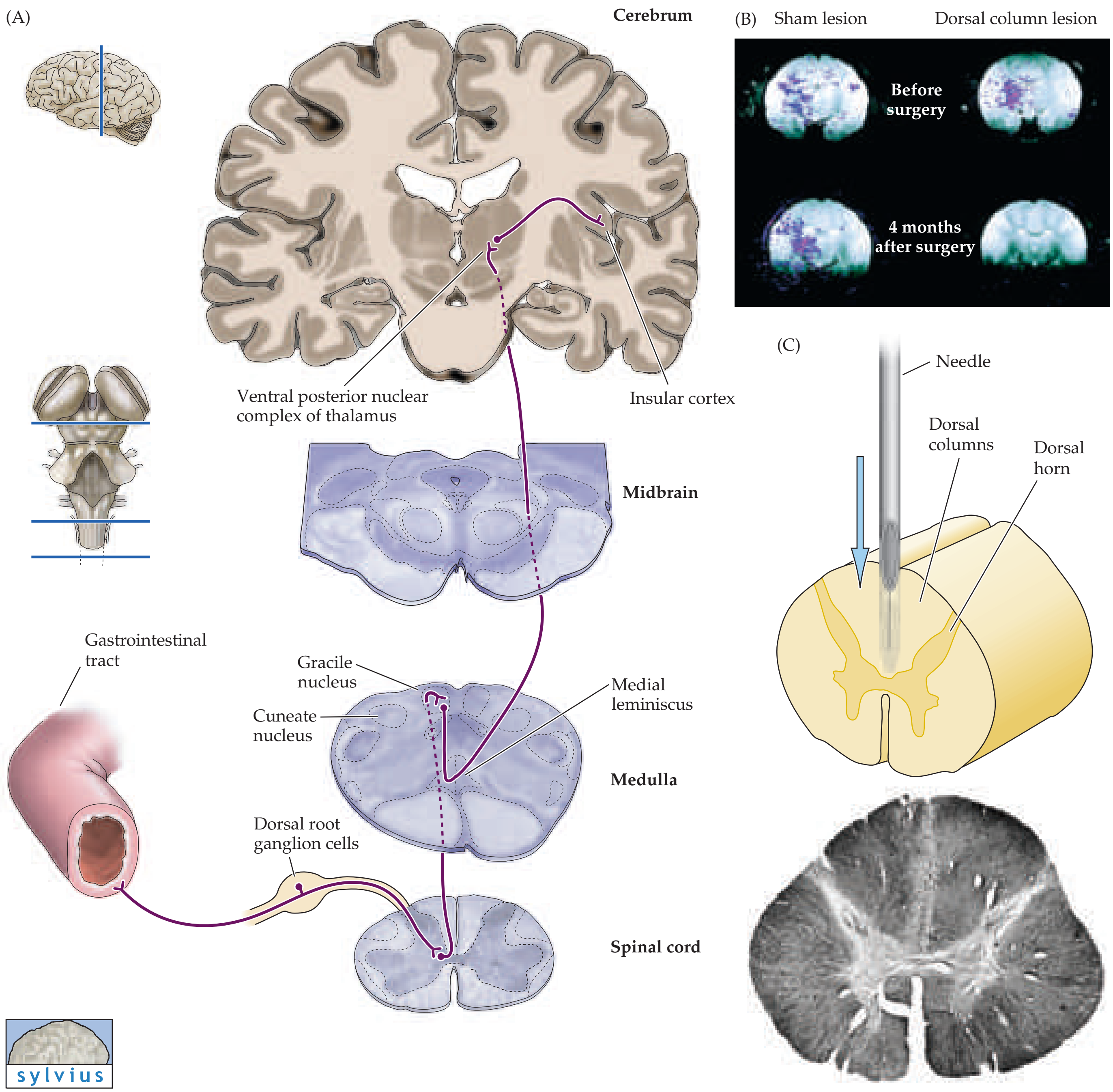

(A)
Cerebrum
Ventral posterior nuclear complex of thalamus
Insular cortex
Midbrain
Gastrointestinal tract
Gracile nucleus
Cuneate nucleus
Medial leminiscus
Medulla
Dorsal root ganglion cells
Spinal cord
sylvius
(B) Sham lesion
Dorsal column lesion
Before surgery
4 months after surgery
(C)
Needle
Dorsal columns
Dorsal horn

(A) A visceral pain pathway in the dorsal-column medial lemniscal system. For simplicity, only the pathways that mediate visceral pain from the pelvis and lower abdomen are illustrated. The mechanosensory component of this system for the discrimination of tactile stimuli and the anterolateral system for the detection of painful and thermal cutaneous stimuli are also shown for comparison (see also Figures 8.6A and 9.3A). (B) Empirical evidence supporting the existence of the visceral pain pathway shown in (A). Increased neural activity was observed with functional MRI techniques in the thalamus of monkeys that were subjected to noxious distention of the colon and rectum, indicating the processing of visceral pain. This activity was abolished by lesion of the dorsal columns at T10, but not by "sham" surgery. (From Willis et al., 1999.) (C) Top, one method of punctate midline myelotomy for the relief of severe visceral pain. Bottom, myelin-stained section of the thoracic spinal cord (T10) from a patient who underwent midline myelotomy for the treatment of colon cancer pain that was not controlled by analgesics. After surgery, the patient experienced relief from pain during the remaining three months of his life. (From Hirshberg et al., 1996; drawing after Nauta et al., 1997.)

representation of pain is the least well documented aspect of the central pathways for nociception, and further studies will be needed to elucidate the contribution of regions outside the somatosensory areas of the parietal lobe. Nevertheless, a prominent role for these areas in the perception of pain is suggested by the fact that ablations of the relevant regions of the parietal cortex do not generally alleviate chronic pain (although they impair contralateral mechanosensory perception, as expected).

Sensitization

Following a painful stimulus associated with tissue damage (e.g., cuts, scrapes, and bruises), , stimuli in the area of the injury and the surrounding region that would ordinarily be perceived as slightly painful are perceived as significantly more so, a phenomenon referred to as **hyperalgesia**. A good example of hyperalgesia is the increased sensitivity to temperature that occurs after a sunburn. This effect is due to changes in neuronal sensitivity that occur at the level of peripheral receptors as well as their central targets.

Peripheral sensitization results from the interaction of nociceptors with the “inflammatory soup” (Figure 9.6) of substances released when tissue is damaged. These products of tissue damage include extracellular protons, arachidonic acid and other lipid metabolites, bradykinin, histamine, serotonin, prostaglandins, nucleotides, and nerve growth factor (NGF), all of which can interact with receptors or ion channels of nociceptive fibers, augmenting their response. For example, the responses of the TRPV1 receptor to heat can be potentiated by direct interaction of the channel with extracellular protons or lipid metabolites. NGF and bradykinin also potentiate the

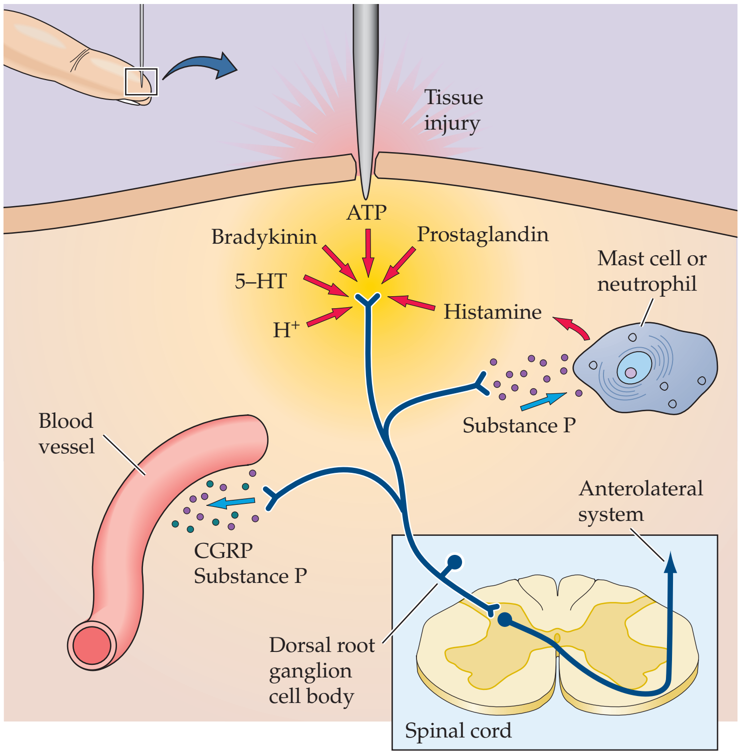


Figure 9.6 Inflammatory response to tissue damage. Substances released by damaged tissues augment the response of nociceptive fibers. In addition, electrical activation of nociceptors causes the release of peptides and neurotransmitters that further contribute to the inflammatory response.

activity of the TRPV1 receptors, but do so indirectly through the actions of separate cell-surface receptors (TrkA and bradykinin receptors respectively) and their associated intracellular signalling pathways. The prostaglandins are thought to contribute to peripheral sensitization by binding to G-protein-coupled receptors that increase levels of cyclic AMP within nociceptors. Prostaglandins also reduce the threshold depolarization required for generating action potentials via phosphorylation of a specific class of TTX-resistant Na channels that are expressed in nociceptors. In addition, electrical activity in the nociceptors causes them to release peptides and neurotransmitters such as substance P, calcitonin-gene–related peptide (CGRP) and ATP which further contribute to the inflammatory response, causing vasodilation, swelling, and the release of histamine from mast cells. The presumed purpose of the complex chemical signaling arising from local damage is not only to protect the injured area (as a result of the painful perceptions produced by ordinary stimuli close to the site of damage), but also to promote healing and guard against infection by means of local effects such as increased blood flow and the migration of white blood cells to the site. Obviously the identification of the components of the inflammatory soup and their mechanisms of action is a fertile area to explore for potential analgesics (i.e., compounds that reduce pain intensity). For example, so-called nonsteroidal anti-inflammatory drugs (NSAIDs), which include aspirin and ibuprofen, act by inhibiting cyclooxygenase (COX), an enzyme important in the biosynthesis of prostaglandins.

Central sensitization refers to an immediate onset, activity dependent increase in the excitability of neurons in the dorsal horn of the spinal cord following high levels of activity in the nociceptive afferents. As a result, activity levels in nociceptive afferents that were subthreshold prior to the sensitizing event, become sufficient to generate action potentials in dorsal horn neurons, contributing to an increase in pain sensitivity. Although central sensitization is triggered in dorsal horn neurons by activity in nociceptors, the effects generalize to other inputs that arise from low threshold mechanoreceptors. Thus, stimuli that under normal conditions would be innocuous (such as brushing the surface of the skin) activate second-order neurons in the dorsal horn that receive nociceptive inputs, and give rise to a sensation of pain. The induction of pain by what is normally an innocuous stimulus is referred to as **allodynia**. This phenomenon typically occurs immediately after the painful event and can outlast the stimulus by several hours.

Like its peripheral counterpart, a number of different mechanisms contribute to central sensitization, and these can be divided broadly into transcription independent and dependent processes. One form of transcription independent central sensitization called "windup" involves a progressive increase in the discharge rate of dorsal horn neurons in response to repeated low frequency activation of nociceptive afferents. A behavioral correlate of the windup phenomenon has been studied by examining the perceived intensity of pain in response to multiple presentations of a noxious stimulus. Although the intensity of the stimulation is constant, the perceived intensity increases with each stimulus presentation. Windup lasts only during the period of stimulation and arises from the summation of the slow synaptic potentials that are evoked in dorsal horn neurons by nociceptive inputs. The sustained depolarization of the dorsal horn neurons results in part from the activation of voltage dependent L-type calcium channels, and from the removal of the Mg block of NMDA receptors, increasing the sensitivity of the

Box D

Phantom Limbs and Phantom Pain

Following the amputation of an extremity, nearly all patients have an illusion that the missing limb is still present. Although this illusion usually diminishes over time, it persists in some degree throughout the amputee's life and can often be reactivated by injury to the stump or other perturbations. Such phantom sensations are not limited to amputated limbs; phantom breasts following mastectomy, phantom genitalia following castration, and phantoms of the entire lower body following spinal cord transection have all been reported. Phantoms are also common after local nerve block for surgery. During recovery from brachial plexus anesthesia, for example, it is not unusual for the patient to experience a phantom arm, perceived as whole and intact, but displaced from the real arm. When the real arm is viewed, the phantom appears to "jump into" the arm and may emerge and reenter intermittently as the anesthesia wears off. These sensory phantoms demonstrate that the central machinery for processing somatic sensory information is not idle in the absence of peripheral stimuli; apparently, the central sensory processing apparatus continues to operate independently of the periphery, giving rise to these bizarre sensations.

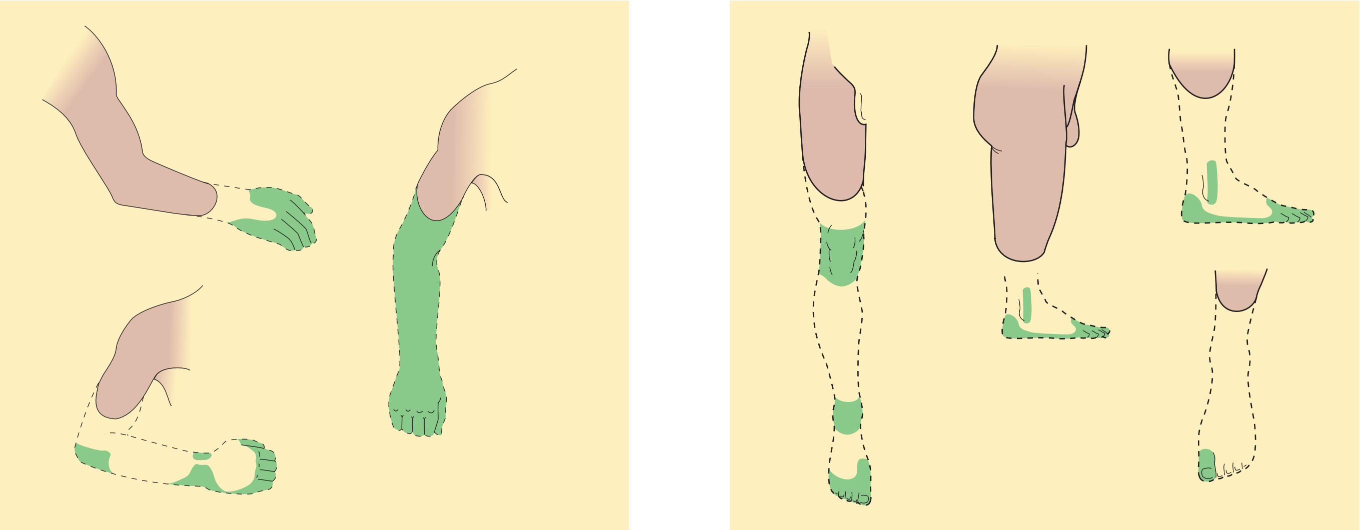
Interestingly, considerable functional reorganization of somatotopic maps in the primary somatosensory cortex occurs in amputees (see Chapter 24). This reorganization starts immediately after the amputation and tends to evolve for several years. One of the effects of this process is that neurons that have lost their original inputs (i.e., from the removed limb) respond to tactile stimulation of other body parts. A surprising consequence is that stimulation of the face, for example, can be experienced as if the missing limb had been touched.

Further evidence that the phenomenon of phantom limb is the result of a central representation is the experience of children born without limbs. Such individuals have rich phantom sensations, despite the fact that a limb never developed. This observation suggests that a full represenation of the body exists independently of the peripheral elements that are mapped. Based on these results, Ronald Melzack proposed that the loss of a limb generates an internal mismatch between the brain's representation of the body and the pattern of peripheral tactile input that reaches the neocortex. The consequence would be an illusory sensation that the missing body part is still present and functional. With time, the brain may adapt to this loss and alter its intrinsic somatic representation to better accord with the new configuration of the body. This change could explain why the phantom sensation appears almost immediately after limb loss, but usually decreases in intensity over time.

Phantoms might simply be a curiosity—or a provocative clue about higher-order somatic sensory processing—were it not for the fact that a substantial number of amputees also develop phantom pain. This common problem is usually described as a tingling or burning sensation in the missing part. Sometimes, however, the sensation becomes a more seri-

the dorsal horn neuron to glutamate, the transmitter in nociceptive afferents. Other forms of central sensitization that last longer than the period of sensory stimulation (such as allodynia) are thought to involve an LTP-like enhancement of postsynaptic potentials (see Chapter 24). The longest lasting forms, resulting from transcription dependent processes, can be elicited by changes in neuronal activity or by humoral signals. Those elicited by neuronal activity are localized to the site of the injury, while humoral activation can lead to more widespread changes. For example, cytokines released from microglia and from other sources promote the widespread transcription of COX-2 and the production of prostaglandins in dorsal horn neurons. As described for nociceptive afferents, increased levels of prostaglandins in CNS neurons augments neuronal excitability. Thus the analgesic effects of drugs that inhibit COX are due to actions in both the periphery and within the dorsal horn.

As injured tissue heals, the sensitization induced by peripheral and central mechanisms typically declines and the theshold for pain returns to



Drawings of phantom arms and legs, based on patients' reports. The phantom is indicated by a dashed line, with the colored regions showing the most vividly experienced parts. Note that some phantoms are telescoped into the stump. (After Solonen, 1962.)

ous pain that patients find increasingly debilitating. Phantom pain is, in fact, one of the more common causes of chronic pain syndromes and is extraordinarily difficult to treat. Because of the widespread nature of central pain processing, ablation of the spinothalamic tract, portions of the thalamus, or even primary sensory cortex does not generally relieve the discomfort felt by these patients.

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preinjury levels. However, when the afferent fibers or central pathways themselves are damaged—a frequent complication in pathological conditions that include diabetes, shingles, AIDs, multiple sclerosis, and stroke—these processes can persist. The resulting condition is refered to as **neuropathic pain,** a chronic, intensely painful experience that is difficult to treat with conventional analgesic medications. (See Box D for a description of neuropathic pain associated with amputation of an extremity.) The pain can arise spontaneously (without a stimulus) or can be produced by mild forms of stimulation that are common to everyday experience, such as the gentle touch and pressure of clothing, or warm and cool temperatures. Patients often describe their experience as a constant burning sensation interrupted by episodes of shooting, stabbing, or electric shocklike jolts. Because the disability and psychological stress associated with chronic neuropathic pain can be severe, much present research is being devoted to better understanding of the mechanisms of peripheral and central sensitization with the hope of more effective therapies for this debilitating syndrome.

Descending Control of Pain Perception

With respect to the *interpretation* of pain, observers have long commented on the difference between the objective reality of a painful stimulus and the subjective response to it. Modern studies of this discrepancy have provided considerable insight into how circumstances affect pain perception and, ultimately, into the anatomy and pharmacology of the pain system.

During World War II, Henry Beecher and his colleagues at Harvard Medical School made a fundamental observation. In the first systematic study of its kind, they found that soldiers suffering from severe battle wounds often experienced little or no pain. Indeed, many of the wounded expressed surprise at this odd dissociation. Beecher, an anesthesiologist, concluded that the perception of pain depends on its context. For instance, the pain of an injured soldier on the battlefield would presumably be mitigated by the imagined benefits of being removed from danger, whereas a similar injury in a domestic setting would present quite a different set of circumstances that could exacerbate the pain (loss of work, financial liability, and so on). Such observations, together with the well-known placebo effect (discussed in the next section), make clear that the perception of pain is subject to central modulation (all sensations are subject to at least some degree of this kind of modification). This statement, incidentally, should not be taken as a vague acknowledgment about the importance of psychological or “top-down” influences on sensory experience. On the contrary, there has been a gradual realization among neuroscientists and neurologists that such “psychological” effects are as real and important as any other neural phenomenon. This appreciation has provided a much more rational view of psychosomatic problems in general, and pain in particular.

The Placebo Effect

The placebo effect is defined as a physiological response following the administration of a pharmacologically inert “remedy.” The word *placebo* means “I will please,” and the placebo effect has a long history of use (and abuse) in medicine. The reality of the effect is undisputed. In one classic study, medical students were given one of two different pills, one said to be a sedative and the other a stimulant. In fact, both pills contained only inert ingredients. Of the students who received the “sedative,” more than two-thirds reported that they felt drowsy, and students who took two such pills felt sleepier than those who had taken only one. Conversely, a large fraction of the students who took the “stimulant” reported that they felt less tired. Moreover, about a third of the entire group reported side effects ranging from headaches and dizziness to tingling extremities and a staggering gait! Only 3 of the 56 students studied reported that the pills they took had no appreciable effect.

In another study of this general sort, 75% of patients suffering from postoperative wound pain reported satisfactory relief after an injection of sterile saline. The researchers who carried out this work noted that the responders were indistinguishable from the nonresponders, both in the apparent severity of their pain and psychological makeup. Most tellingly, this placebo effect in postoperative patients could be blocked by naloxone, a competitive antagonist of opiate receptors, indicating a substantial pharmacological basis for the pain relief experienced (see the next section). A common misunderstanding about the placebo effect is the view that patients who respond to a therapeutically meaningless reagent are not suffering real pain, but only “imagining” it; this is certainly not the case.

Among other things, the placebo effect probably explains the efficacy of acupuncture anesthesia and the analgesia that can sometimes be achieved by hypnosis. In China, surgery has often been carried out under the effect of a needle (often carrying a small electrical current) inserted at locations dictated by ancient acupuncture charts. Before the advent of modern anesthetic techniques, operations such as thyroidectomies for goiter were commonly done without extraordinary discomfort, particularly among populations where stoicism was the cultural norm.

The mechanisms of pain amelioration on the battlefield, in acupuncture anesthesia, and with hypnosis are presumably related. Although the mechanisms by which the brain affects the perception of pain are only beginning to be understood, the effect is neither magical nor a sign of a suggestible intellect. In short, the placebo effect is quite real.

The Physiological Basis of Pain Modulation

Understanding the central modulation of pain perception (on which the placebo effect is presumably based) was greatly advanced by the finding that electrical or pharmacological stimulation of certain regions of the midbrain produces relief of pain. This analgesic effect arises from activation of descending pain-modulating pathways that project to the dorsal horn of the spinal cord (as well as to the spinal trigeminal nucleus) and regulate the transmission of information to higher centers (Figure 9.7A). One of the major brainstem regions that produce this effect is located in the periaqueductal gray of the midbrain. Electrical stimulation at this site in experimental animals not only produces analgesia by behavioral criteria, but also demonstrably inhibits the activity of nociceptive projection neurons in the dorsal horn of the spinal cord.

Further studies of descending pathways to the spinal cord that regulate the transmission of nociceptive information have shown that they arise from a number of brainstem sites, including the parabrachial nucleus, the dorsal raphe, and locus coeruleus and the medullary reticular formation (see Figure 9.7A). The analgesic effects of stimulating the periaqueductal gray are mediated through these brainstem sites. These centers employ a wealth of different neurotransmitters (noradrenaline, serotonin, dopamine, histamine, acetylcholine) and can exert both facilitatory and inhibitory effects on the the activity of neurons in the dorsal horn. The complexity of these interactions is made even greater by the fact that descending projections can exert their effects on a variety of sites within the dorsal horn including the synaptic terminals of nociceptive afferents, excitatory and inhibitory interneurons, the synaptic terminals of the other descending pathways, as well as by contacting the projection neurons themselves. Although these descending projections were originally viewed as a mechanism that served primarily to inhibit the transmission of nociceptive signals, it is now evident that these projections provide a balance of facilitatory and inhibitory influences that ultimately determines the efficacy of nociceptive transmission.

In addition to descending projections, local interactions between mechanoreceptive afferents and neural circuits within the dorsal horn can modulate the transmission of nociceptive information to higher centers (Figure 9.7B). These interactions are thought to explain the ability to reduce the sensation of sharp pain by activating low-threshold mechanoreceptors: If you crack your shin or stub a toe, a natural (and effective) reaction is to vigor-

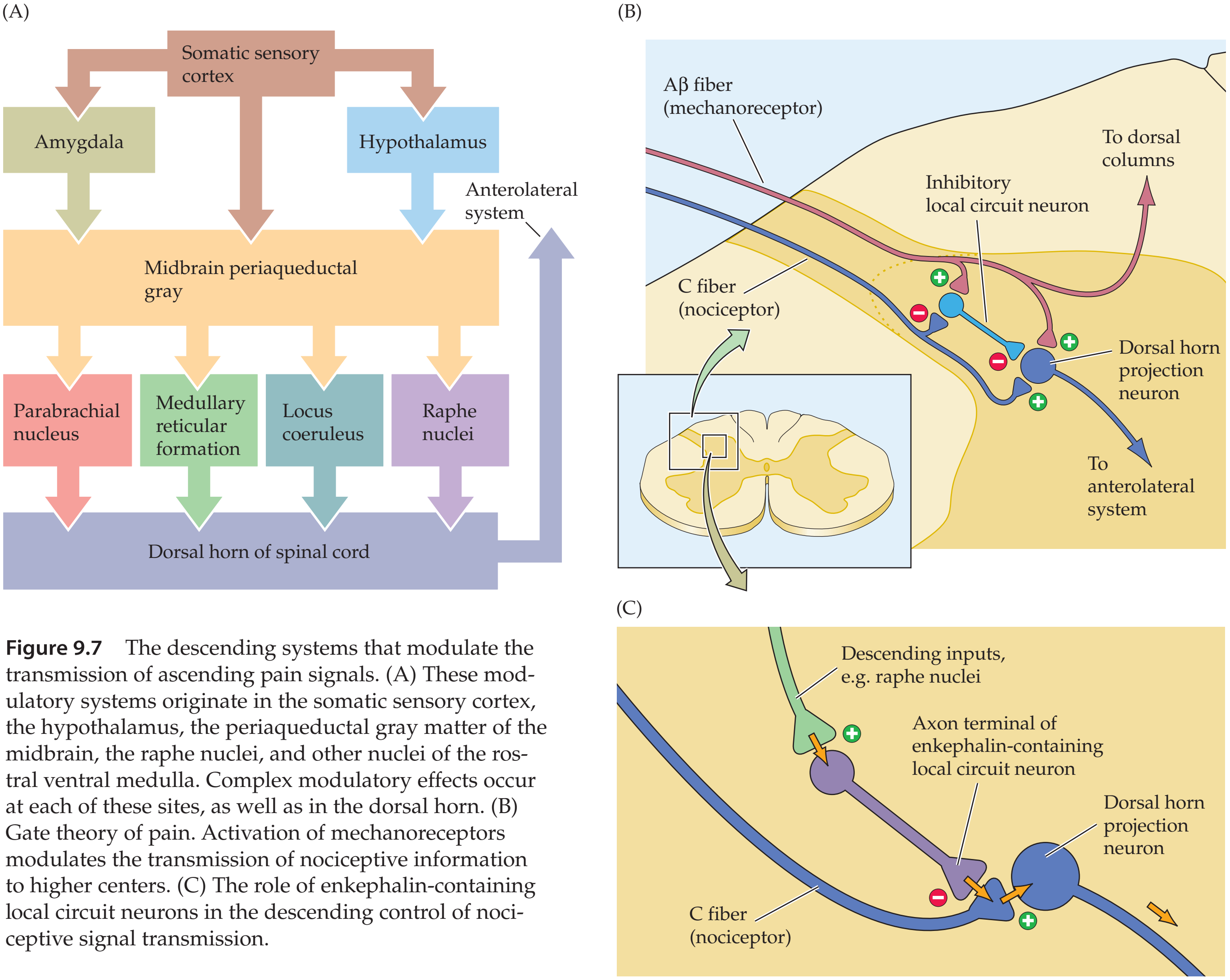
(A)
Somatic sensory cortex
Amygdala
Hypothalamus
Anterolateral system
Midbrain periaqueductal gray
Parabrachial nucleus
Medullary reticular formation
Locus coeruleus
Raphe nuclei
Dorsal horn of spinal cord
(B)
Aβ fiber (mechanoreceptor)
To dorsal columns
Inhibitory local circuit neuron
C fiber (nociceptor)
Dorsal horn projection neuron
To anterolateral system
(C)
Descending inputs, e.g. raphe nuclei
Axon terminal of enkephalin-containing local circuit neuron
Dorsal horn projection neuron
C fiber (nociceptor)

Figure 9.7 The descending systems that modulate the transmission of ascending pain signals. (A) These modulatory systems originate in the somatic sensory cortex, the hypothalamus, the periaqueductal gray matter of the midbrain, the raphe nuclei, and other nuclei of the rostral ventral medulla. Complex modulatory effects occur at each of these sites, as well as in the dorsal horn. (B) Gate theory of pain. Activation of mechanoreceptors modulates the transmission of nociceptive information to higher centers. (C) The role of enkephalin-containing local circuit neurons in the descending control of nociceptive signal transmission.

sylvius

ously rub the site of injury for a minute or two. Such observations, buttressed by experiments in animals, led Ronald Melzack and Patrick Wall to propose that the flow of nociceptive information through the spinal cord is modulated by concomitant activation of the large myelinated fibers associated with low-threshold mechanoreceptors. Even though further investigation led to modification of some of the original propositions in Melzack and Wall's **gate theory of pain**, the idea stimulated a great deal of work on pain modulation and has emphasized the importance of synaptic interactions within the dorsal horn for modulating the perception of pain intensity.

The most exciting advance in this long-standing effort to understand central mechanisms of pain regulation has been the discovery of **endogenous opioids**. For centuries it had been apparent that opium derivatives such as morphine are powerful analgesics—indeed, they remain a mainstay of analgesic therapy today. Modern animal studies have shown that a variety of brain regions are susceptible to the action of opiate drugs, particularly—and significantly—the periaqueductal gray matter and other sources of descending projections. There are, in addition, opiate-sensitive neurons within the dorsal horn of the spinal cord. In other words, the areas that produce analgesia when stimulated are also responsive to exogenously administered opiates. It seems likely, then, that opiate drugs act at most or all of the sites shown in Figure 9.7 in producing their dramatic pain-relieving effects.

The analgesic action of opiates implied the existence of specific brain and spinal cord receptors for these drugs long before the receptors were actually found during the 1960s and 1970s. Since such receptors are unlikely to exist for the purpose of responding to the administration of opium and its derivatives, the conviction grew that there must be *endogenous* compounds for which these receptors had evolved (see Chapter 6). Several categories of endogenous opioids have now been isolated from the brain and intensively studied. These agents are found in the same regions that are involved in the modulation of nociceptive afferents, although each of the families of endogenous opioid peptides has a somewhat different distribution. All three of the major groups (**enkephalins**, **endorphins**, and **dynorphins**; see Table 6.2) are present in the periaqueductal gray matter. The enkephalins and dynorphins have also been found in the rostral ventral medulla and in the spinal cord regions involved in the modulation of pain.

One of the most compelling examples of the mechanism by which endogenous opiates modulate transmission of nociceptive information occurs at the first synapse in the pain pathway between nociceptive afferents and projection neurons in the dorsal horn of the spinal cord (see Figure 9.7B). A class of enkephalin-containing local circuit neurons within the dorsal horn synapses with the axon terminals of nociceptive afferents, which synapse in turn with dorsal horn projection neurons. The release of enkephalin onto the nociceptive terminals inhibits their release of neurotransmitter onto the projection neuron, reducing the level of activity that is passed on to higher centers. Enkephalin-containing local circuit neurons are themselves the targets of descending projections, thus providing a powerful mechanism by which higher centers can decrease the activity relayed by nociceptive afferents.

A particularly impressive aspect of this story is the wedding of physiology, pharmacology, and clinical research to yield a much richer understanding of the intrinsic modulation of pain. This information has finally begun to explain the subjective variability of painful stimuli and the striking dependence of pain perception on the context of the experience. Precisely how pain is modulated is being explored in many laboratories at present, motivated by the tremendous clinical (and economic) benefits that would accrue from still deeper knowledge of the pain system and its molecular underpinnings.

Summary

Whether from a structural or functional perspective, pain is an extraordinarily complex sensory modality. Because of the importance of warning an animal about dangerous circumstances, the mechanisms and pathways that subserve nociception are widespread and redundant. A distinct set of pain afferents with membrane receptors known as nociceptors transduces noxious stimulation and conveys this information to neurons in the dorsal horn of the spinal cord. The major central pathway responsible for transmitting the discriminative aspects of pain (location, intensity and quality) differs from the mechanosensory pathway primarily in that the central axons of dorsal root ganglion cells synapse on second-order neurons in the dorsal horn; the axons of the second-order neurons then cross the midline in the spinal cord and ascend to thalamic nuclei that relay information to the somatic sensory cortex of the postcentral gyrus. Additional pathways involving a number of centers in the brainstem, thalamus, and cortex mediate the affective and motivational responses to painful stimuli. Descending pathways interact with local circuits in the spinal cord to regulate the transmission of nociceptive signals to higher centers. Tremendous progress in understanding pain has been made in the last 25 years, and much more seems likely, given the importance of the problem. No patients are more distressed—or more difficult to treat—than those with chronic pain. Indeed, some aspects of pain seem much more destructive to the sufferer than required by any physiological purposes. Perhaps such seemingly excessive effects are a necessary but unfortunate by-product of the protective benefits of this vital sensory modality.

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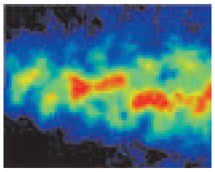
Chapter 10



Vision: The Eye

Overview

The human visual system is extraordinary in the quantity and quality of information it supplies about the world. A glance is sufficient to describe the location, size, shape, color, and texture of objects and, if the objects are moving, their direction and speed. Equally remarkable is the fact that visual information can be discerned over a wide range of stimulus intensities, from the faint light of stars at night to bright sunlight. The next two chapters describe the molecular, cellular, and higher-order mechanisms that allow us to see. The first steps in the process of seeing involve transmission and refraction of light by the optics of the eye, the transduction of light energy into electrical signals by photoreceptors, and the refinement of these signals by synaptic interactions within the neural circuits of the retina.

Anatomy of the Eye

The eye is a fluid-filled sphere enclosed by three layers of tissue (Figure 10.1). Only the innermost layer of the eye, the **retina**, contains neurons that are sensitive to light and are capable of transmitting visual signals to central targets. The immediately adjacent layer of tissue includes three distinct but continuous structures collectively referred to as the **uveal tract**. The largest component of the uveal tract is the **choroid**, which is composed of a rich capillary bed (important for nourishing the photoreceptors of the retina) as well as a high concentration of the light absorbing pigment melanin. Extending from the choroid near the front of the eye is the **ciliary body**, a ring of tissue that encircles the lens and consists of a muscular component that is important for adjusting the refractive power of the lens, and a vascular component (the so-called ciliary processes) that produces the fluid that fills the front of the eye. The most anterior component of the uveal tract is the **iris**, the colored portion of the eye that can be seen through the cornea. It contains two sets of muscles with opposing actions, which allow the size of the **pupil** (the opening in its center) to be adjusted under neural control. The **sclera** forms the outermost tissue layer of the eye and is composed of a tough white fibrous tissue. At the front of the eye, however, this opaque outer layer is transformed into the **cornea**, a specialized transparent tissue that permits light rays to enter the eye.

Beyond the cornea, light rays pass through two distinct fluid environments before striking the retina. In the **anterior chamber**, just behind the cornea and in front of the lens, lies **aqueous humor**, a clear, watery liquid that supplies nutrients to both of these structures. Aqueous humor is produced by the ciliary processes in the **posterior chamber** (the region between

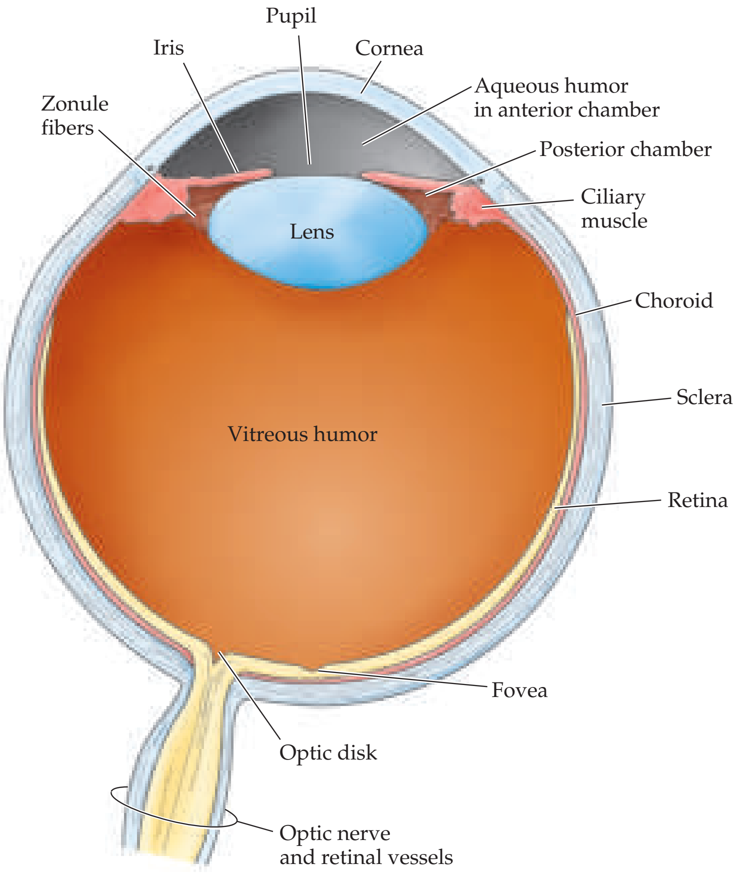

Pupil
Iris
Cornea
Zonule fibers
Aqueous humor in anterior chamber
Posterior chamber
Ciliary muscle
Lens
Choroid
Sclera
Vitreous humor
Retina
Fovea
Optic disk
Optic nerve and retinal vessels

Figure 10.1 Anatomy of the human eye.

the lens and the iris) and flows into the anterior chamber through the pupil. The amount of fluid produced by the ciliary processes is substantial: it is estimated that the entire volume of fluid in the anterior chamber is replaced 12 times a day. Thus the rates of a aqueous humor production must be balanced by comparable rates of drainage from the anterior chamber in order to ensure a constant intraocular pressure. A specialized meshwork of cells that lies at the junction of the iris and the cornea (a region called the **limbus**) is responsible for aqueous drainage. Failure of adequate drainage results in a disorder known as **glaucoma**, in which high levels of intraocular pressure can reduce the blood supply to the eye and eventually damage retinal neurons.

The space between the back of the lens and the surface of the retina is filled with a thick, gelatinous substance called the **vitreous humor**, which accounts for about 80% of the volume of the eye. In addition to maintaining the shape of the eye, the vitreous humor contains phagocytic cells that remove blood and other debris that might otherwise interfere with light transmission. The housekeeping abilities of the vitreous humor are limited, however, as a large number of middle-aged and elderly individuals with vitreal “floaters” will attest. Floaters are collections of debris too large for phagocytic consumption that therefore remain to cast annoying shadows on the retina; they typically arise when the aging vitreous membrane pulls away from the overly long eyeball of myopic individuals (Box A).

The Formation of Images on the Retina

Normal vision requires that the optical media of the eye be transparent, and both the **cornea** and the **lens** are remarkable examples of tissue specializations that achieve a level of transparency that rivals that found in inorganic materials such as glass. Not surprisingly, alterations in the composition of the cornea or the lens can significantly reduce their transparency and have serious consequences for visual perception. Indeed, **cataracts** (opacities in the lens) account for roughly half the cases of blindness in the world, and almost everyone over the age of 70 will experience some loss of transparency in the lens that ultimately degrades the quality of visual experience. Fortunately, there are successful surgical treatments for cataracts that can restore vision in most cases. Furthermore, the recognition that a major factor in the production of cataracts is exposure to ultraviolet (UV) solar radiation has heightened public awareness of the need to protect the lens (and the retina) by reducing UV exposure through the use of sunglasses.

Beyond efficiently transmitting light energy, the primary function of the optical components of the eye is to achieve a focused image on the surface of the retina. The cornea and the lens are primarily responsible for the refraction (bending) of light that is necessary for formation of focused images on the photoreceptors of the retina (Figure 10.2). The cornea contributes most of the necessary refraction, as can be appreciated by considering the hazy, out-of-focus images experienced when swimming underwater. Water, unlike air, has a refractive index close to that of the cornea; as a result, immersion in water virtually eliminates the refraction that normally occurs at the air/cornea interface; thus the image is no longer focused on the retina. The lens has considerably less refractive power than the cornea; however, the refraction supplied by the lens is adjustable, allowing objects at various distances from the observer to be brought into sharp focus.

Dynamic changes in the refractive power of the lens are referred to as **accommodation**. When viewing distant objects, the lens is made relatively thin and flat and has the least refractive power. For near vision, the lens becomes thicker and rounder and has the most refractive power (see Figure 10.2). These changes result from the activity of the **ciliary muscle** that surrounds the lens. The lens is held in place by radially arranged connective tissue bands (called zonule fibers) that are attached to the ciliary muscle. The shape of the lens is thus determined by two opposing forces: the elasticity of the lens, which tends to keep it rounded up (removed from the eye, the lens

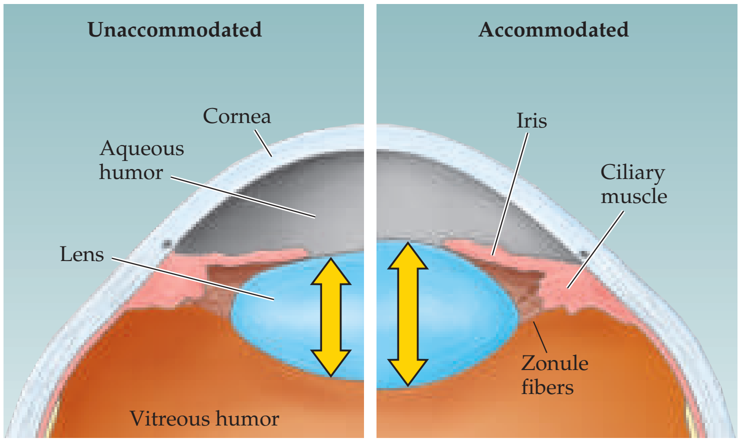


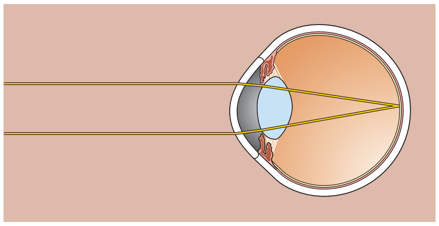
Figure 10.2 Diagram showing the anterior part of the human eye in the unaccommodated (left) and accommodated (right) state. Accommodation for focusing on near objects involves the contraction of the ciliary muscle, which reduces the tension in the zonule fibers and allows the elasticity of the lens to increase its curvature.

Box A

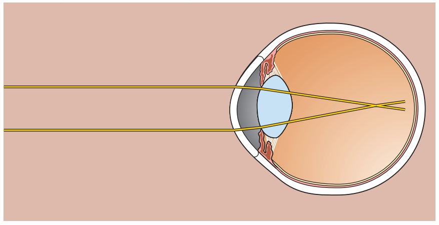
Myopia and Other Refractive Errors

Optical discrepancies among the various components of the eye cause a majority of the human population to have some form of refractive error, called *ametropia*. People who are unable to bring distant objects into clear focus are said to be nearsighted, or myopic (Figures A and B). *Myopia* can be caused by the corneal surface being too curved, or by the eyeball being too long. In either case, with the lens as flat as it can be, the image of distant objects focuses in front of, rather than on, the retina. People who are unable to focus on near objects are said to be farsighted, or hyperopic. *Hyperopia* can be caused by the eyeball being too short or the refracting system too weak (Figure C). Even with the lens in its most rounded-up state, the image is out of focus on the retinal surface (focusing at some point behind it). Both myopia and hyperopia are correctable by appropriate lenses—concave (minus) and convex (plus), respectively—or by the increasingly popular technique of corneal surgery.

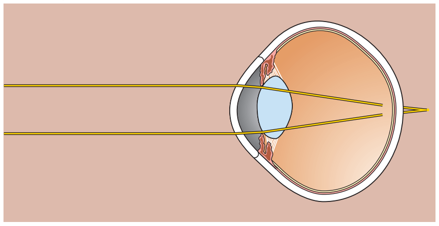
(A) Emmetropia (normal)



(B) Myopia (nearsighted)



(C) Hyperopia (farsighted)

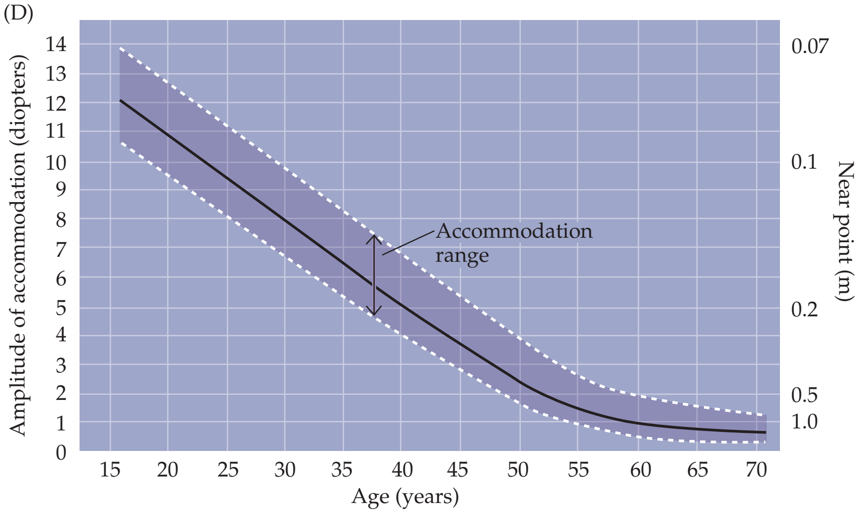


Refractive errors. (A) In the normal eye, with ciliary muscles relaxed, an image of a distant object is focused on the retina. (B) In myopia, light rays are focused in front of the retina. (C) In hyperopia, images are focused at a point beyond the retina.

Myopia, or nearsightedness, is by far the most common ametropia; an estimated 50% of the population in the United States is affected. Given the large number of people who need glasses, contact lenses, or surgery to correct this refractive error, one naturally wonders how nearsighted people coped before spectacles were invented only a few centuries ago. From what is now known about myopia, most people's vision may have been considerably better in ancient times. The basis for this assertion is the surprising finding that the growth of the eyeball is strongly influenced by focused light falling on the retina. This phenomenon was first described in 1977 by Torsten Wiesel and Elio Raviola at Harvard Medical School, who studied monkeys reared with their lids sutured (the same approach used to demonstrate the effects of visual deprivation on cortical connections in the visual system; see Chapter 23), a procedure that deprives the eye of focused retinal images. They found that animals growing to maturity under these conditions show an elongation of the eyeball. The effect of focused light deprivation appears to be a local one, since the abnormal growth of the eye occurs in experimental animals even if the optic nerve is cut. Indeed, if only a portion of the retinal surface is deprived of focused light, then only that region of the eyeball grows abnormally.

Although the mechanism of light-mediated control of eye growth is not fully understood, many experts now believe that the prevalence of myopia is due to some aspect of modern civilization—perhaps learning to read and write at an early age—that interferes with the normal feedback control of vision on eye development, leading to abnormal elongation of the eyeball. A corollary of this hypothesis is that if children (or, more likely, their parents) wanted to improve their vision, they might be able to do so by practicing far vision to counterbalance the near work "overload." Practically, of

becomes spheroidal), and the tension exerted by the zonule fibers, which tends to flatten it. When viewing distant objects, the force from the zonule fibers is greater than the elasticity of the lens, and the lens assumes the flatter shape appropriate for distance viewing. Focusing on closer objects requires relaxing the tension in the zonule fibers, allowing the inherent elasticity of the lens to increase its curvature. This relaxation is accomplished by the sphincter-like contraction of the ciliary muscle. Because the ciliary muscle forms a ring around the lens, when the muscle contracts, the attachment points of the zonule fibers move toward the central axis of the eye, thus



(D) Changes in the ability of the lens to round up (accommodate) with age. The graph also shows how the near point (the closest point to the eye that can be brought into focus) changes. Accommodation, which is an optical measurement of the refractive power of the lens, is given in diopters. (After Westheimer, 1974.)

course, most people would probably choose wearing glasses or contacts or having corneal surgery rather than indulging in the onerous daily practice that would presumably be required. Not everyone agrees, however, that such a remedy would be effective, and a number of investigators (and drug companies) are exploring the possibility of pharmacological intervention during the period of childhood when abnormal eye growth is presumed to occur. In any event, it is a remarkable fact that deprivation of focused light on the retina causes a compensatory growth of the eye and that this feedback loop is so easily perturbed.

Even people with normal (emmetropic) vision as young adults eventually experience difficulty focusing on near objects. One of the many consequences of aging is that the lens loses its elasticity; as a result, the maximum curvature the lens can achieve when the ciliary muscle contracts is gradually reduced. The near point (the closest point that can be brought into clear focus) thus recedes, and objects (such as this book) must be farther and farther away from the eye in order to focus them on the retina. At some point, usually during early middle age, the accommodative ability of the eye is so reduced that near vision tasks like reading become difficult or impossible (Figure D). This condition is referred to as presbyopia, and can be corrected by convex lenses for near-vision tasks, or by bifocal lenses if myopia is also present (which requires a negative correction). Bifocal correction presents a particular problem for those who prefer contact lenses. Because contact lenses float on the surface of the cornea, having the distance correction above and the near correction below (as in conventional bifocal glasses) doesn't work (although "omnifocal" contact lenses have recently been used with some success). A surprisingly effective solution to this problem for some contact lens wearers has been to put a near correcting lens in one eye and a distance correcting lens in the other! The success of this approach is another testament to the remarkable ability of the visual system to adjust to a wide variety of unusual demands.

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reducing the tension on the lens. Unfortunately, changes in the shape of the lens are not always able to produce a focused image on the retina, in which case a sharp image can be focused only with the help of additional corrective lenses (see Box A).

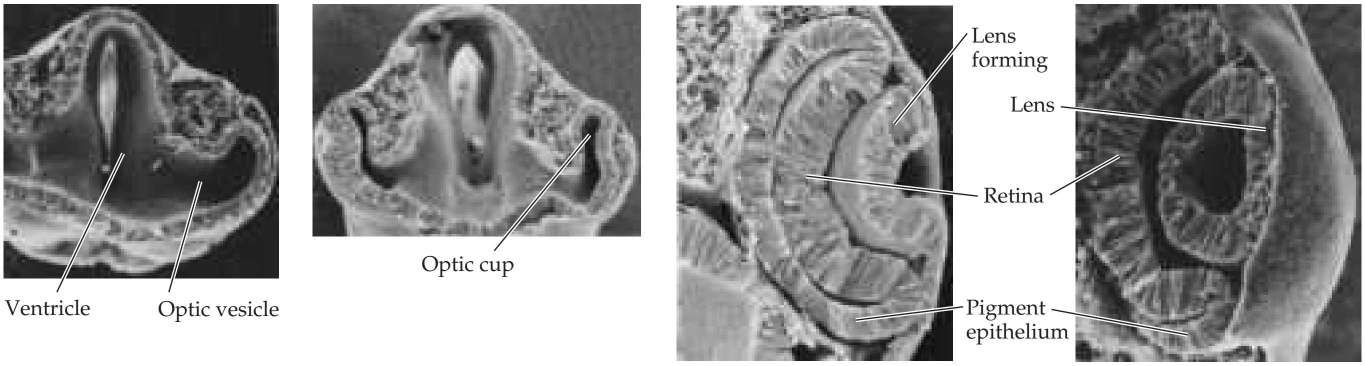
Adjustments in the size of the pupil also contribute to the clarity of images formed on the retina. Like the images formed by other optical instruments, those generated by the eye are affected by spherical and chromatic aberrations, which tend to blur the retinal image. Since these aberrations are greatest for light rays that pass farthest from the center of the lens, narrowing the pupil reduces both spherical and chromatic aberration, just as closing the iris diaphragm on a camera lens improves the sharpness of a photographic image. Reducing the size of the pupil also increases the depth of field—that is, the distance within which objects are seen without blurring. However, a small pupil also limits the amount of light that reaches the retina, and, under conditions of dim illumination, visual acuity becomes limited by the number of available photons rather than by optical aberrations. An adjustable pupil thus provides an effective means of reducing optical aberrations, while maximizing depth of field to the extent that different levels of illumination permit. The size of the pupil is controlled by innervation from both sympathetic and parasympathetic divisions of the visceral motor system, which are in turn modulated by several brainstem centers (see Chapters 19 and 20).

The Retina

Despite its peripheral location, the **retina** or neural portion of the eye, is actually part of the central nervous system. During development, the retina forms as an outpocketing of the diencephalon, called the optic vesicle, which undergoes invagination to form the optic cup (Figure 10.3; see also Chapter 21). The inner wall of the optic cup gives rise to the retina, while the outer wall gives rise to the **retinal pigment epithelium**. This epithelium is a thin melanin-containing structure that reduces backscattering of light that enters the eye; it also plays a critical role in the maintenance of photoreceptors, renewing photopigments and phagocytosing the photoreceptor disks, whose turnover at a high rate is essential to vision.

Consistent with its status as a full-fledged part of the central nervous system, the retina comprises complex neural circuitry that converts the graded electrical activity of photoreceptors into action potentials that travel to the brain via axons in the optic nerve. Although it has the same types of functional elements and neurotransmitters found in other parts of the central nervous system, the retina comprises fewer classes of neurons, and these are arranged in a manner that has been less difficult to unravel than the circuits in other areas of the brain. There are five types of neurons in the retina: **photoreceptors, bipolar cells, ganglion cells, horizontal cells**, and **amacrine cells**. The cell bodies and processes of these neurons are stacked in alternating layers, with the cell bodies located in the inner nuclear, outer nuclear, and ganglion cell layers, and the processes and synaptic contacts located in the inner plexiform and outer plexiform layers (Figure 10.4). A direct three-

Figure 10.3 Development of the human eye. (A) The retina develops as an outpocketing from the neural tube, called the optic vesicle. (B) The optic vesicle invaginates to form the optic cup. (C, D) The inner wall of the optic cup becomes the neural retina, while the outer wall becomes the pigment epithelium. (A–C from Hilfer and Yang, 1980; D courtesy of K. Tosney.)


(A) 4-mm embryo
(B) 4.5-mm embryo
(C) 5-mm embryo
(D) 7-mm embryo

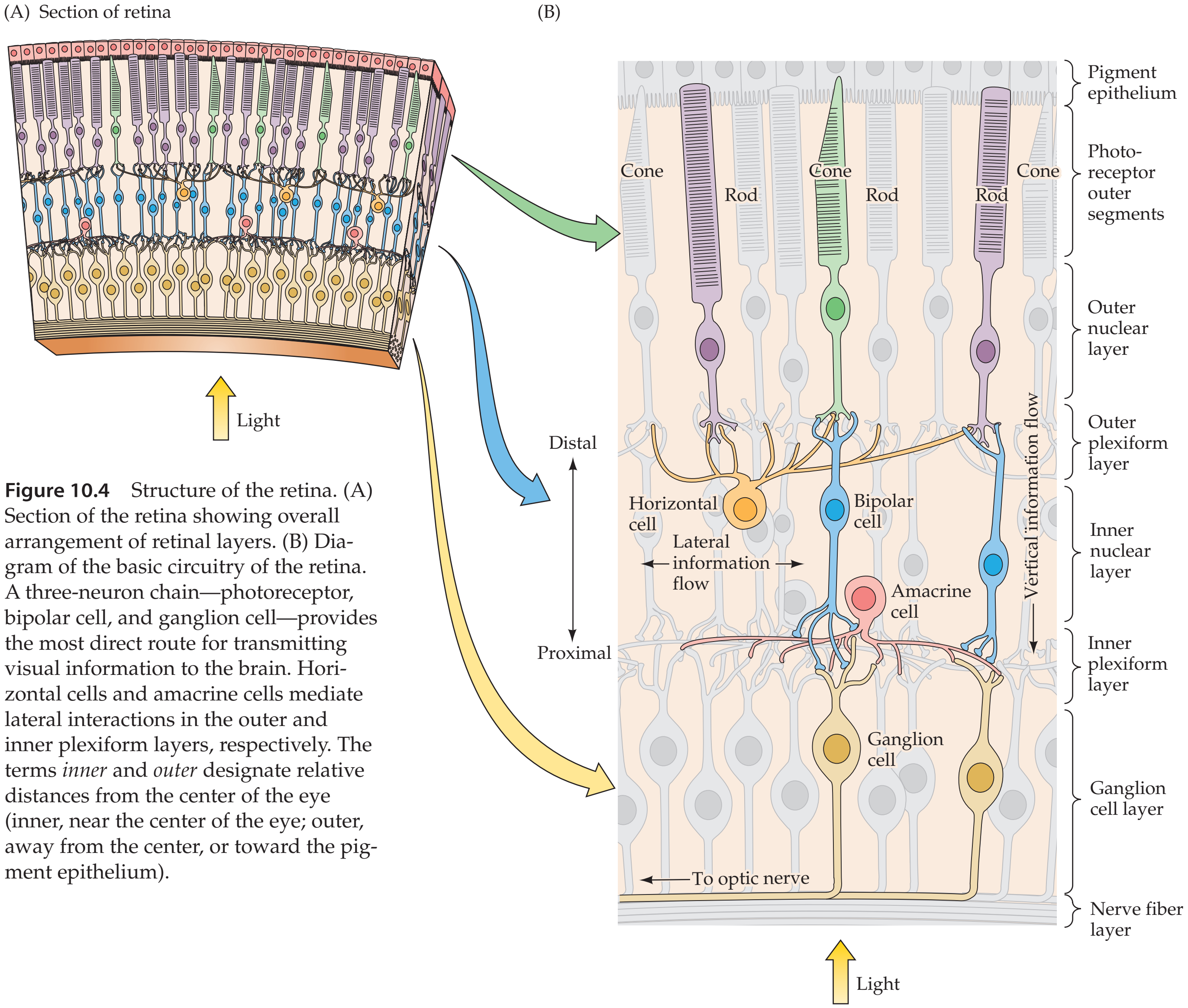

(A) Section of retina
Light
(B)
Cone
Rod
Cone
Rod
Rod
Cone
Distal
Proximal
Horizontal cell
Lateral information flow
Bipolar cell
Amacrine cell
Vertical information flow
Ganglion cell
To optic nerve
Light
Pigment epithelium
Photo-receptor outer segments
Outer nuclear layer
Outer plexiform layer
Inner nuclear layer
Inner plexiform layer
Ganglion cell layer
Nerve fiber layer

Figure 10.4 Structure of the retina. (A) Section of the retina showing overall arrangement of retinal layers. (B) Diagram of the basic circuitry of the retina. A three-neuron chain—photoreceptor, bipolar cell, and ganglion cell—provides the most direct route for transmitting visual information to the brain. Horizontal cells and amacrine cells mediate lateral interactions in the outer and inner plexiform layers, respectively. The terms *inner* and *outer* designate relative distances from the center of the eye (inner, near the center of the eye; outer, away from the center, or toward the pigment epithelium).

neuron chain—photoreceptor cell to bipolar cell to ganglion cell—is the major route of information flow from photoreceptors to the optic nerve.

There are two types of photoreceptors in the retina: **rods** and **cones**. Both types have an outer segment composed of membranous disks that contain light-sensitive photopigment and lies adjacent to the pigment epithelium, and an inner segment that contains the cell nucleus and gives rise to synaptic terminals that contact bipolar or horizontal cells (see also Figure 10.8). Absorption of light by the photopigment in the outer segment of the photoreceptors initiates a cascade of events that changes the membrane potential of the receptor, and therefore the amount of neurotransmitter released by the photoreceptor synapses onto the cells they contact. The synapses between photoreceptor terminals and bipolar cells (and horizontal cells) occur in the outer plexiform layer; more specifically, the cell bodies of photoreceptors make up the outer nuclear layer, whereas the cell bodies of bipolar cells lie in the inner nuclear layer. The short axonal processes of bipolar cells make synaptic contacts in turn on the dendritic processes of ganglion cells in the inner plexiform layer. The much larger axons of the ganglion cells form the **optic**

nerve and carry information about retinal stimulation to the rest of the central nervous system.

The two other types of neurons in the retina, **horizontal cells** and **amacrine cells**, have their cell bodies in the inner nuclear layer and have processes that are limited to the outer and inner plexiform layers respectively (see Figure 10.4). The processes of horizontal cells enable lateral interactions between photoreceptors and bipolar cells that maintain the visual system's sensitivity to luminance contrast over a wide range of light intensities. The processes of amacrine cells are postsynaptic to bipolar cell terminals and presynaptic to the dendrites of ganglion cells. Different subclasses of amacrine cells are thought to make distinct contributions to visual function. One class of amacrine cells, for example, plays an important role in transforming the sustained responses of bipolar cells to step changes in light intensity into transient onset or offset responses exhibited by some types of ganglion cells. Another type serves as an obligatory step in the pathway that transmits information from rod photoreceptors to retinal ganglion cells. The variety of amacrine cell subtypes illustrates the more general rule that although there are only five basic retinal cell types, there can be considerable diversity within a given cell type. This diversity is also a hallmark of retinal ganglion cells and the basis for pathways that convey different sorts of information to central targets in a parallel manner (see Chapter 11).

At first glance, the spatial arrangement of retinal layers seems counterintuitive, since light rays must pass through various non-light-sensitive elements of the retina as well as the retinal vasculature (which branches extensively on the inner surface of the retina—see Figure 11.1) before reaching the outer segments of the photoreceptors, where photons are absorbed (Figure 10.4). The reason for this curious feature of retinal organization lies in the special relationship that exists among the outer segments of the photoreceptors, the pigment epithelium, and the underlying choroid. Recall that the outer segments contain membranous disks that house the light-sensitive photopigment and other proteins involved in the transduction process. These disks are formed near the inner segment of the photoreceptor and move toward the tip of the outer segment, where they are shed. The pigment epithelium plays an essential role in removing the expended receptor disks; this is no small task, since all the disks in the outer segments are replaced every 12 days. In addition, the pigment epithelium contains the biochemical machinery that is required to regenerate photopigment molecules after they have been exposed to light. Finally, the capillaries in the choroid underlying the pigment epithelium are the primary source of nourishment for retinal photoreceptors. These functional considerations presumably explain why rods and cones are found in the outermost rather than the innermost layer of the retina. They also explain why disruptions in the normal relationships between the pigment epithelium and retinal photoreceptors such as those that occur in retinitis pigmentosa have severe consequences for vision (Box B).

Phototransduction

In most sensory systems, activation of a receptor by the appropriate stimulus causes the cell membrane to depolarize, ultimately stimulating an action potential and transmitter release onto the neurons it contacts. In the retina, however, photoreceptors do not exhibit action potentials; rather, light activation causes a graded change in membrane potential and a corresponding change in the rate of transmitter release onto postsynaptic neurons. Indeed,

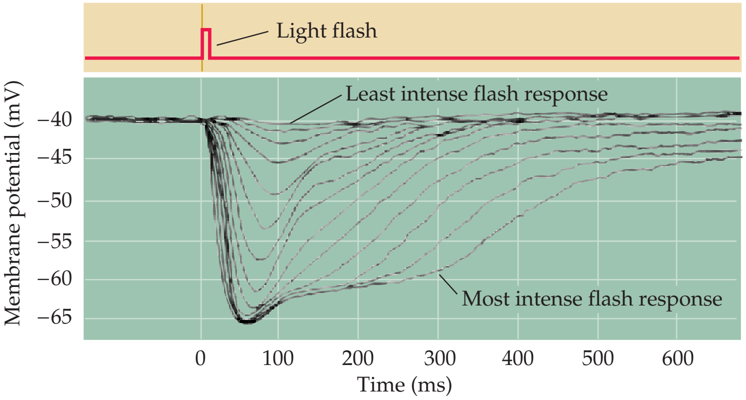


Figure 10.5 An intracellular recording from a single cone stimulated with different amounts of light (the cone has been taken from the turtle retina, which accounts for the relatively long time course of the response). Each trace represents the response to a brief flash that was varied in intensity. At the highest light levels, the response amplitude saturates (at about –65 mV). The hyperpolarizing response is characteristic of vertebrate photoreceptors; interestingly, some invertebrate photoreceptors depolarize in response to light. (After Schnapf and Baylor, 1987.)

much of the processing within the retina is mediated by graded potentials, largely because action potentials are not required to transmit information over the relatively short distances involved.

Perhaps even more surprising is that shining light on a photoreceptor, either a rod or a cone, leads to membrane *hyperpolarization* rather than depolarization (Figure 10.5). In the dark, the receptor is in a depolarized state, with a membrane potential of roughly –40 mV (including those portions of the cell that release transmitters). Progressive increases in the intensity of illumination cause the potential across the receptor membrane to become more negative, a response that saturates when the membrane potential reaches about –65 mV. Although the sign of the potential change may seem odd, the only logical requirement for subsequent visual processing is a consistent relationship between luminance changes and the rate of transmitter release from the photoreceptor terminals. As in other nerve cells, transmitter release from the synaptic terminals of the photoreceptor is dependent on voltage-sensitive Ca^{2+} channels in the terminal membrane. Thus, in the dark, when photoreceptors are relatively depolarized, the number of open Ca^{2+} channels in the synaptic terminal is high, and the rate of transmitter release is correspondingly great; in the light, when receptors are hyperpolarized, the number of open Ca^{2+} channels is reduced, and the rate of transmitter release is also reduced. The reason for this unusual arrangement compared to other sensory receptor cells is not known.

The relatively depolarized state of photoreceptors in the dark depends on the presence of ion channels in the outer segment membrane that permit Na^+ and Ca^{2+} ions to flow into the cell, thus reducing the degree of inside negativity (Figure 10.6). The probability of these channels in the outer segment being open or closed is regulated in turn by the levels of the nucleotide cyclic guanosine monophosphate (cGMP) (as in many other second messenger systems; see Chapter 7). In darkness, high levels of cGMP in the outer segment keep the channels open. In the light, however, cGMP levels drop and some of the channels close, leading to hyperpolarization of the outer segment membrane, and ultimately the reduction of transmitter release at the photoreceptor synapse.

The series of biochemical changes that ultimately leads to a reduction in cGMP levels begins when a photon is absorbed by the photopigment in the receptor disks. The photopigment contains a light-absorbing chromophore (**retinal**, an aldehyde of vitamin A) coupled to one of several possible proteins called **opsins** that tune the molecule's absorption of light to a particular region of the spectrum. Indeed, it is the different protein component of

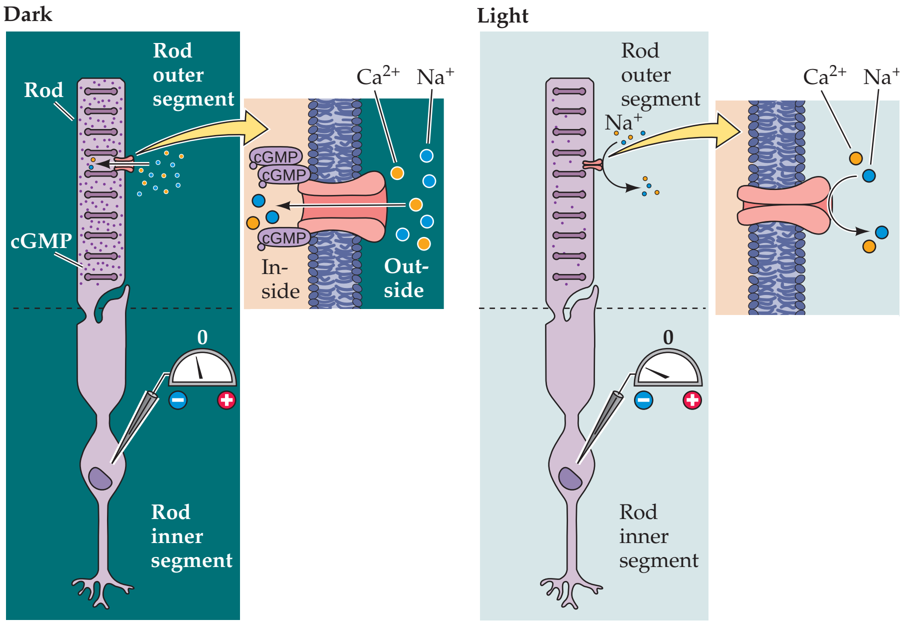

Dark
Rod
Rod outer segment
cGMP
cGMP
cGMP
cGMP
Ca^{2+}
Na^{+}
In-side
Out-side
0
Rod inner segment
Light
Rod outer segment
Na^{+}
Ca^{2+}
Na^{+}
0
Rod inner segment

Figure 10.6 Cyclic GMP-gated channels in the outer segment membrane are responsible for the light-induced changes in the electrical activity of photoreceptors (a rod is shown here, but the same scheme applies to cones). In the dark, cGMP levels in the outer segment are high; this molecule binds to the Na^{+}-permeable channels in the membrane, keeping them open and allowing sodium (and other cations) to enter, thus depolarizing the cell. Exposure to light leads to a decrease in cGMP levels, a closing of the channels, and receptor hyperpolarization.

the photopigment in rods and cones that contributes to the functional specialization of these two receptor types. Most of what is known about the molecular events of phototransduction has been gleaned from experiments in rods, in which the photopigment is **rhodopsin** (Figure 10.7A). When the retinal moiety in the rhodopsin molecule absorbs a photon, its configuration changes from the 11-*cis* isomer to all-*trans* retinal; this change then triggers a series of alterations in the protein component of the molecule (Figure 10.7B). The changes lead, in turn, to the activation of an intracellular messenger called **transducin**, which activates a phosphodiesterase that hydrolyzes

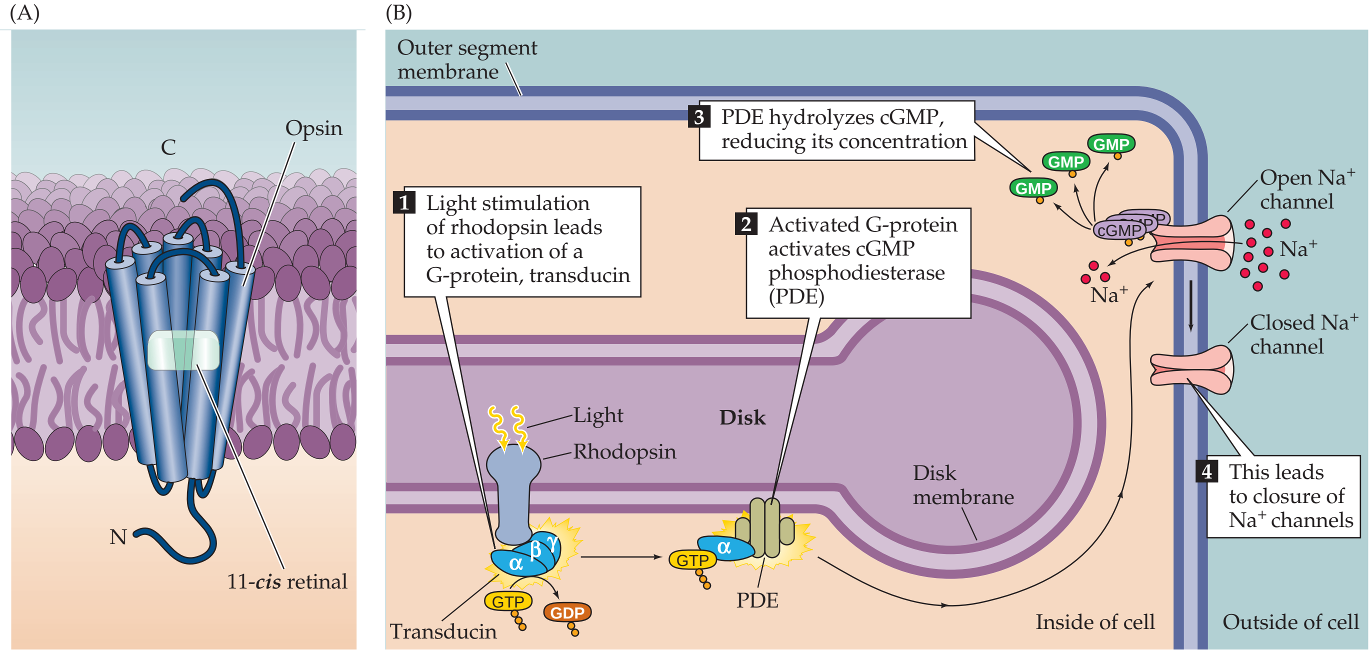

(A)
C
Opsin
N
11-*cis* retinal
(B)
Outer segment membrane
3 PDE hydrolyzes cGMP, reducing its concentration
GMP
GMP
GMP
cGMP
Open Na^{+} channel
Na^{+}
Na^{+}
1 Light stimulation of rhodopsin leads to activation of a G-protein, transducin
2 Activated G-protein activates cGMP phosphodiesterase (PDE)
Closed Na^{+} channel
Light
Rhodopsin
Disk
Disk membrane
4 This leads to closure of Na^{+} channels
α
β
γ
GTP
GDP
Transducin
GTP
α
PDE
Inside of cell
Outside of cell

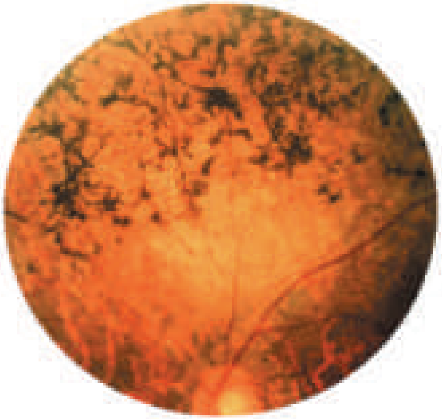
Figure 10.7 Details of phototransduction in rod photoreceptors. (A) The molecular structure of rhodopsin, the pigment in rods. (B) The second messenger cascade of phototransduction. Light stimulation of rhodopsin in the receptor disks leads to the activation of a G-protein (transducin), which in turn activates a phosphodiesterase (PDE). The phosphodiesterase hydrolyzes cGMP, reducing its concentration in the outer segment and leading to the closure of sodium channels in the outer segment membrane.

Box B
Retinitis Pigmentosa

Retinitis pigmentosa (**RP**) refers to a heterogeneous group of hereditary eye disorders characterized by progressive vision loss due to a gradual degeneration of photoreceptors. An estimated 100,000 people in the United States have RP. In spite of the name, inflammation is not a prominent part of the disease process; instead the photoreceptor cells appear to die by apoptosis (determined by the presence of DNA fragmentation).

Classification of this group of disorders under one rubric is based on the clinical features commonly observed in these patients. The hallmarks of RP are night blindness, a reduction of peripheral vision, narrowing of the retinal vessels, and the migration of pigment from disrupted retinal pigment epithelium into the retina, forming clumps of various sizes, often next to retinal blood vessels (see figure).

Typically, patients first notice difficulty seeing at night due to the loss of rod photoreceptors; the remaining cone photoreceptors then become the mainstay of visual function. Over many years, the cones also degenerate, leading to a progressive loss of vision. In most RP patients, visual field defects begin in the midperiphery, between 30° and 50° from the point of foveal fixation. The defective regions gradually enlarge, leaving islands of vision in the periphery and a constricted central field—a condition known as tunnel vision. When the visual field contracts to 20° or less and/or central vision is 20/200 or worse, the patient is categorized as legally blind.



Characteristic appearance of the retina in patients with retinitis pigmentosa. Note the dark clumps of pigment that are the hallmark of this disorder.

Inheritance patterns indicate that RP can be transmitted in an X-linked (XLRP), autosomal dominant (ADRP), or recessive (ARRP) manner. In the United States, the percentage of these genetic types is estimated to be 9%, 16%, and 41%, respectively. When only one member of a pedigree has RP, the case is classified as "simplex," which accounts for about a third of all cases.

Among the three genetic types of RP, ADRP is the mildest. These patients often retain good central vision until 60 years of age or older. In contrast, patients with the XLRP form of the disease are usually legally blind by 30 to 40 years of age. However, the severity and age of onset of the symptoms varies greatly among patients with the same type of RP, and even within the same family (when, presumably, all the affected members have the same genetic mutation).

To date, RP-inducing mutations of 30 genes have been identified. Many of these genes encode photoreceptor-specific proteins, several being associated with phototransduction in the rods. Among the latter are genes for rhodopsin, subunits of the cGMP phosphodiesterase, and the cGMP-gated channel. Multiple mutations have been found in each of these cloned genes. For example, in the case of the rhodopsin gene, 90 different mutations have been identified among ADRP patients.

The heterogeneity of RP at all levels, from genetic mutations to clinical symptoms, has important implications for understanding the pathogenesis of the disease and designing therapies. Given the complex molecular etiology of RP, it is unlikely that a single cellular mechanism will explain the disease in all cases. Regardless of the specific mutation or causal sequence, the vision loss that is most critical to RP patients is due to the gradual degeneration of cones. In many cases, the protein that the RP-causing mutation affects is not even expressed in the cones; the prime example is rhodopsin—the rod-specific visual pigment. Therefore, the loss of cones may be an indirect result of a rod-specific mutation. In consequence, understanding and treating this disease presents a particularly difficult challenge.

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The Foundation Fighting Blindness of Hunt Valley, MD, maintains a web site that provides updated information about many forms of retinal degeneration: www.blindness.org

RetNet provides updated information, including references to original articles, on genes and mutations associated with retinal diseases: www.sph.uth.tmc.edu/RetNet

cGMP. All of these events take place within the disk membrane. The hydrolysis by phosphodiesterase at the disk membrane lowers the concentration of cGMP throughout the outer segment, and thus reduces the number of cGMP molecules that are available for binding to the channels in the surface of the outer segment membrane, leading to channel closure.

One of the important features of this complex biochemical cascade initiated by photon capture is that it provides enormous signal amplification. It has been estimated that a single light-activated rhodopsin molecule can activate 800 transducin molecules, roughly eight percent of the transducin molecules on the disk surface. Although each transducin molecule activates only one phosphodiesterase molecule, each of these is in turn capable of catalyzing the breakdown of as many as six cGMP molecules. As a result, the absorption of a single photon by a rhodopsin molecule results in the closure of approximately 200 ion channels, or about 2% of the number of channels in each rod that are open in the dark. This number of channel closures causes a net change in the membrane potential of about 1 mV.

Equally important is the fact that the magnitude of this amplification varies with the prevailing levels of illumination, a phenomenon known as **light adaptation**. At low levels of illumination, photoreceptors are the most sensitive to light. As levels of illumination increase, sensitivity decreases, preventing the receptors from saturating and thereby greatly extending the range of light intensities over which they operate. The concentration of Ca^{2+} in the outer segment appears to play a key role in the light-induced modulation of photoreceptor sensitivity. The cGMP-gated channels in the outer segment are permeable to both Na^+ and Ca^{2+}; thus, light-induced closure of these channels leads to a net decrease in the internal Ca^{2+} concentration. This decrease triggers a number of changes in the phototransduction cascade, all of which tend to reduce the sensitivity of the receptor to light. For example, the decrease in Ca^{2+} increases the activity of quanylate cyclase, the cGMP synthesizing enzyme, leading to an increase in cGMP levels. Likewise, the decrease in Ca^{2+} increases the affinity of the cGMP-gated channels for cGMP, reducing the impact of the light-induced reduction of cGMP levels. The regulatory effects of Ca^{2+} on the phototransduction cascade are only one part of the mechanism that adapts retinal sensitivity to background levels of illumination; another important contribution comes from neural interactions between horizontal cells and photoreceptor terminals (see below).

Once initiated, additional mechanisms limit the duration of this amplifying cascade and restore the various molecules to their inactivated states. The protein **arrestin**, for instance, blocks the ability of activated rhodopsin to activate transducin, and facilitates the breakdown of activated rhodopsin. The all-*trans* retinal then dissociates from the opsin, diffuses into the cytosol of the outer segment, is converted to all-*trans* retinol and is transported out of the outer segment and into the pigment epithelium, where appropriate enzymes ultimately convert it to 11-*cis* retinal. After it is transported back into the outer segment, the 11-*cis* retinal recombines with opsin in the receptor disks. The recycling of rhodopsin is critically important for maintaining the light sensitivity of photoreceptors. Even under intense levels of illumination, the rate of regeneration is sufficient to maintain a significant number of active photopigment molecules.

Functional Specialization of the Rod and Cone Systems

The two types of photoreceptors, rods and cones, are distinguished by shape (from which they derive their names), the type of photopigment they con-

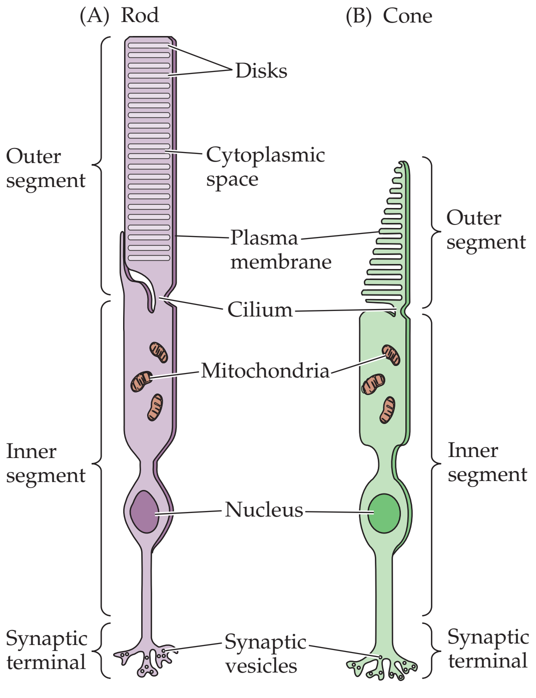

Figure 10.8 Structural differences between rods and cones. Although generally similar in structure, rods (A) and cones (B) differ in their size and shape, as well as in the arrangement of the membranous disks in their outer segments.

tain, distribution across the retina, and pattern of synaptic connections (Figure 10.8). These properties reflect the fact that the rod and cone systems (the receptors and their connections within the retina) are specialized for different aspects of vision. The rod system has very low spatial resolution but is extremely sensitive to light; it is therefore specialized for sensitivity at the expense of resolution. Conversely, the cone system has very high spatial resolution but is relatively insensitive to light; it is therefore specialized for acuity at the expense of sensitivity. The properties of the cone system also allow humans and many other animals to see color.

The range of illumination over which the rods and cones operate is shown in Figure 10.9. At the lowest levels of light, only the rods are activated. Such rod-mediated perception is called **scotopic vision**. The difficulty of making fine visual discriminations under very low light conditions where only the rod system is active is a common experience. The problem is primarily the poor resolution of the rod system (and, to a lesser degree, the fact that there is no perception of color in dim light because the cones are not involved to a significant degree). Although cones begin to contribute to visual perception at about the level of starlight, spatial discrimination at this light level is still very poor. As illumination increases, cones become more and more dominant in determining what is seen, and they are the major determinant of perception under relatively bright conditions such as normal indoor lighting or sunlight. The contributions of rods to vision drops out nearly entirely in so-called **photopic vision** because their response to light saturates—that is, the membrane potential of individual rods no longer varies as a function of illumination because all of the membrane channels are closed (see Figure 10.5). **Mesopic vision** occurs in levels of light at which both rods and cones contribute—at twilight, for example. From these considerations it should be clear that most of what we think of as normal "seeing" is mediated by the cone system, and that loss of cone function is devastating, as occurs in

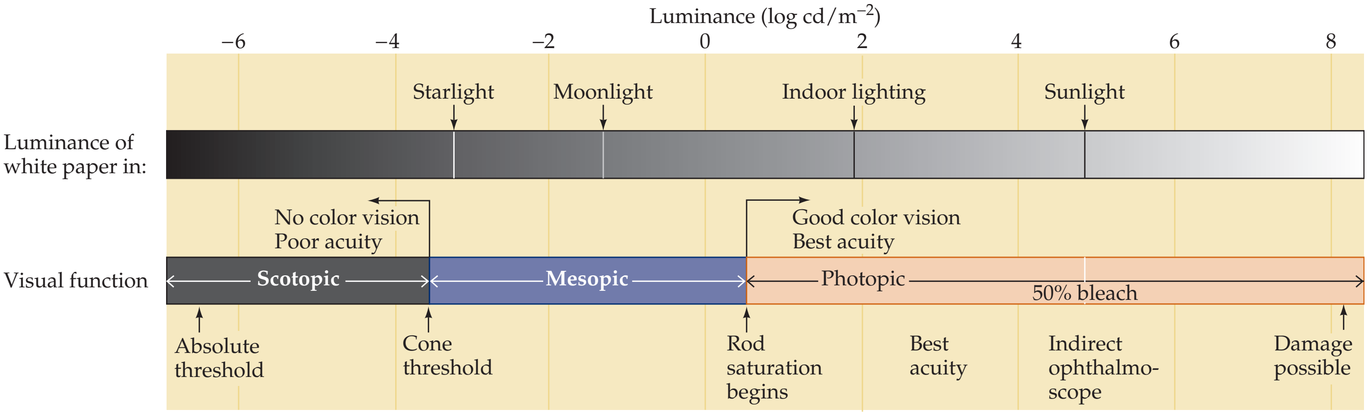

Figure 10.9 The range of luminance values over which the visual system operates. At the lowest levels of illumination, only rods are activated. Cones begin to contribute to perception at about the level of starlight and are the only receptors that function under relatively bright conditions.

elderly individuals suffering from macular degeneration (Box C). People who have lost cone function are legally blind, whereas those who have lost rod function only experience difficulty seeing at low levels of illumination (night blindness; see Box B).

Differences in the transduction mechanisms utilized by the two receptor types is a major factor in the ability of rods and cones to respond to different ranges of light intensity. For example, rods produce a reliable response to a single photon of light, whereas more than 100 photons are required to produce a comparable response in a cone. It is not, however, that cones fail to effectively capture photons. Rather, the change in current produced by single photon capture in cones is comparatively small and difficult to distinguish from noise. Another difference is that the response of an individual cone does not saturate at high levels of steady illumination, as does the rod response. Although both rods and cones adapt to operate over a range of luminance values, the adaptation mechanisms of the cones are more effective. This difference in adaptation is apparent in the time course of the response of rods and cones to light flashes. The response of a cone, even to a bright light flash that produces the maximum change in photoreceptor current, recovers in about 200 milliseconds, more than four times faster than rod recovery.

The arrangement of the circuits that transmit rod and cone information to retinal ganglion cells also contributes to the different characteristics of scotopic and photopic vision. In most parts of the retina, rod and cone signals converge on the same ganglion cells; i.e., individual ganglion cells respond to both rod and cone inputs, depending on the level of illumination. The early stages of the pathways that link rods and cones to ganglion cells, however, are largely independent. For example, the pathway from rods to ganglion cells involves a distinct class of bipolar cell (called rod bipolar) that, unlike cone bipolar cells, does not contact retinal ganglion cells. Instead, rod bipolar cells synapse with the dendritic processes of a specific class of amacrine cell that makes gap junctions and chemical synapses with the terminals of cone bipolars; these processes, in turn, make synaptic contacts on the dendrites of ganglion cells in the inner plexiform layer. As a consequence, the circuits linking the rods and cones to retinal ganglion cells differ dramatically in their degree of convergence. Each rod bipolar cell is contacted by a number of rods, and many rod bipolar cells contact a given amacrine cell. In contrast, the cone system is much less convergent. Thus, each retinal ganglion cell that dominates central vision (called midget gan-

Box C

Macular Degeneration

An estimated six million people in the United States suffer from a condition known as **age-related macular degeneration** (**AMD**), which causes a progressive loss of central vision. Since central vision is critical for sight, diseases that affect the macula (see Figure 11.1) severely limit the ability to perform visual tasks. Indeed, AMD is the most common cause of vision loss in people over age 55, and its incidence is rising with the increasing percentage of elderly individuals in the population.

The underlying problem, which remains poorly understood, is degeneration of the photoreceptors. Usually, patients first notice a blurring of central vision when performing tasks such as reading. Images may also appear distorted. A graph paper-like chart known as the Amsler grid is used as a simple test for early signs of AMD. By focusing on a marked spot in the middle of the grid, the patient can assess whether the parallel and perpendicular lines on the grid appear blurred or distorted. Blurred central vision often progresses to having blind spots within central vision, and in most cases both eyes are eventually involved.

Although the risk of developing AMD clearly increases with age, the causes of the disease are not known. Various studies have implicated hereditary factors, cardiovascular disease, environmental factors such as smoking and light exposure, and nutritional causes. Indeed, it may be that all these contribute to the risk of developing AMD.

In descriptive terms, macular degeneration is broadly divided into two types. In the *exudative-neovascular form*, or "wet" AMD, which accounts for 10% of all cases, abnormal blood vessel growth occurs under the macula. These blood vessels leak fluid and blood into the retina and cause damage to the photoreceptors. Wet AMD tends to progress rapidly and can cause severe damage; rapid loss of central vision may occur over just a few months. The treatment for this form of the disease is laser therapy. By transferring thermal energy, the laser beam destroys the leaky blood vessels under the macula, thus slowing the rate of vision loss. A disadvantage of this approach is that the high thermal energy delivered by the beam also destroys nearby healthy tissue. An improvement in the laser treatment of AMD involves a light-activated drug to target abnormal blood vessels. Once the drug is administered, relatively low energy laser pulses aimed at the abnormal blood vessels are delivered to stimulate the drug, which in turn destroys the abnormal blood vessels with minimal damage to the surrounding tissue.

The remaining 90% of AMD cases are the nonexudative, or "dry" form. In these patients there is a gradual disappearance of the retinal pigment epithelium, resulting in circumscribed areas of atrophy. Since photoreceptor loss follows the disappearance of the pigment epithelium, the affected retinal areas have little or no visual function. Vision loss from dry AMD occurs more gradually, typically over the course of many years. These patients usually retain some central vision, although the loss can be severe enough to compromise performance of tasks that require seeing details. Unfortunately, at the present time there is no treatment for dry AMD. A radical and quite fascinating new approach that offers some promise entails surgically repositioning the retina away from the abnormal area.

Occasionally, macular degeneration occurs in much younger individuals. Many of these cases are caused by various mutations, each with its own clinical manifestations and genetic cause. The most common form of juvenile macular degeneration is known as *Stargardt disease*, which is inherited as an autosomal recessive. Patients are usually diagnosed before they reach the age of 20. Although the progression of vision loss is variable, most of these patients are legally blind by age 50. Mutations that cause Stargardt disease have been identified in the *ABCR* gene, which codes for a protein that transports retinoids across the photoreceptor membrane. Thus, the visual cycle of photopigment regeneration may be disrupted in this form of macular degeneration, presumably by dysfunctional proteins encoded by the abnormal gene. Interestingly, the *ABCR* gene is expressed only in rods, suggesting that the cones may have their own visual cycle enzymes.

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glion cells) receives input from only one cone bipolar cell, which, in turn, is contacted by a single cone. Convergence makes the rod system a better detector of light, because small signals from many rods are pooled to generate a large response in the bipolar cell. At the same time, convergence reduces the spatial resolution of the rod system, since the source of a signal in a rod bipolar cell or retinal ganglion cell could have come from anywhere within a relatively large area of the retinal surface. The one-to-one relationship of cones to bipolar and ganglion cells is, of course, just what is required to maximize acuity.

Anatomical Distribution of Rods and Cones

The distribution of rods and cones across the surface of the retina also has important consequences for vision (Figure 10.10). Despite the fact that perception in typical daytime light levels is dominated by cone-mediated vision, the total number of rods in the human retina (about 90 million) far exceeds the number of cones (roughly 4.5 million). As a result, the density of rods is much greater than cones throughout most of the retina. However, this relationship changes dramatically in the **fovea**, a highly specialized region of the central retina that measures about 1.2 millimeters in diameter (Figure 10.11). In the fovea, cone density increases almost 200-fold, reaching, at its center, the highest receptor packing density anywhere in the retina. This high density is achieved by decreasing the diameter of the cone outer segments such that foveal cones resemble rods in their appearance. The increased density of cones in the fovea is accompanied by a sharp decline in the density of rods. In fact, the central 300 µm of the fovea, called the **foveola**, is totally rod-free.

The extremely high density of cone receptors in the fovea, and the one-to-one relationship with bipolar cells and retinal ganglion cells (see earlier), endows this component of the cone system with the capacity to mediate high visual acuity. As cone density declines with eccentricity and the degree of convergence onto retinal ganglion cells increases, acuity is markedly reduced. Just 6° eccentric to the line of sight, acuity is reduced by 75%, a fact

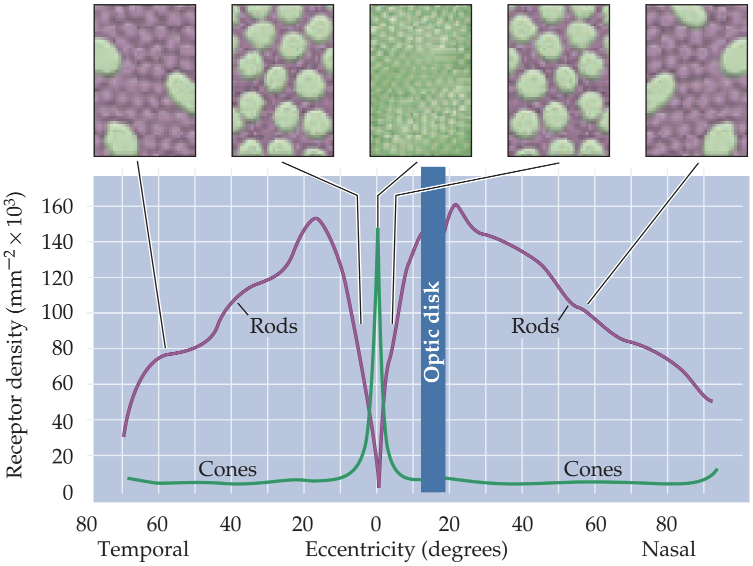

Figure 10.10 Distribution of rods and cones in the human retina. Graph illustrates that cones are present at a low density throughout the retina, with a sharp peak in the center of the fovea. Conversely, rods are present at high density throughout most of the retina, with a sharp decline in the fovea. Boxes at top illustrate the appearance of face on sections through the outer segments of the photoreceptors at different eccentricities. The increased density of cones in the fovea is accompanied by a striking reduction in the diameter of their outer segments.

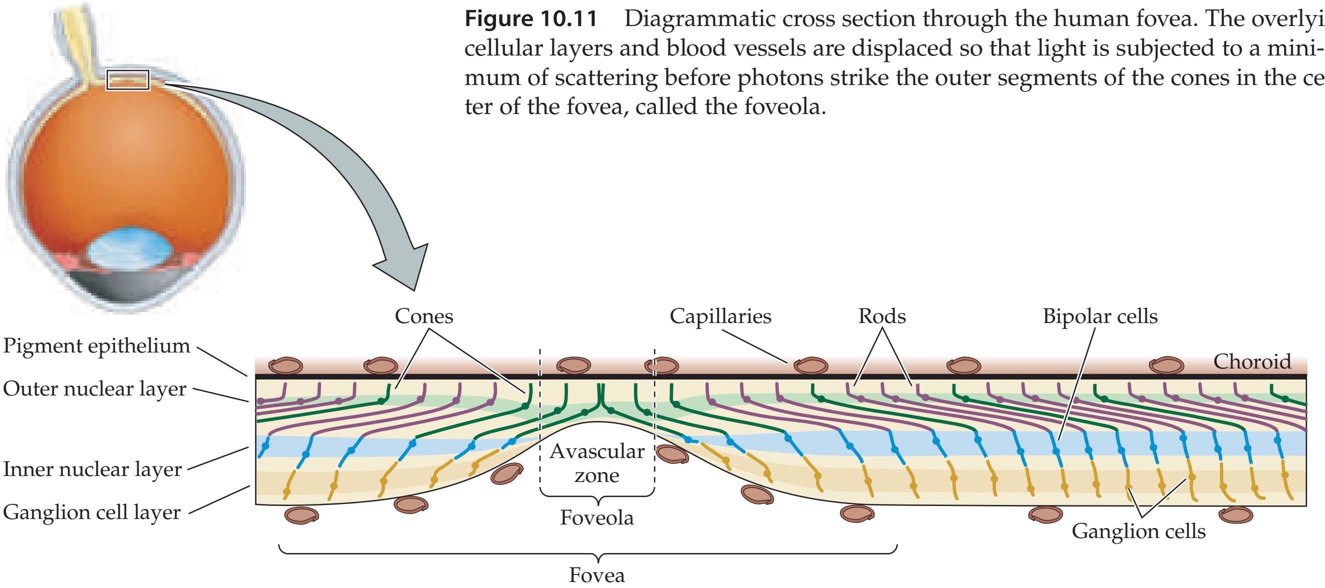

Figure 10.11 Diagrammatic cross section through the human fovea. The overlying cellular layers and blood vessels are displaced so that light is subjected to a minimum of scattering before photons strike the outer segments of the cones in the center of the fovea, called the foveola.

that can be readily appreciated by trying to read the words on any line of this page beyond the word being fixated on. The restriction of highest acuity vision to such a small region of the retina is the main reason humans spend so much time moving their eyes (and heads) around—in effect directing the foveas of the two eyes to objects of interest (see Chapter 19). It is also the reason why disorders that affect the functioning of the fovea have such devastating effects on sight (see Box C). Conversely, the exclusion of rods from the fovea, and their presence in high density away from the fovea, explain why the threshold for detecting a light stimulus is lower outside the region of central vision. It is easier to see a dim object (such as a faint star) by looking slightly away from it, so that the stimulus falls on the region of the retina that is richest in rods (see Figure 10.10).

Another anatomical feature of the fovea (which literally means "pit") that contributes to the superior acuity of the cone system is that the layers of cell bodies and processes that overlie the photoreceptors in other areas of the retina are displaced around the fovea, and especially the foveola (see Figure 10.11). As a result, photons are subjected to a minimum of scattering before they strike the photoreceptors. Finally, another potential source of optical distortion that lies in the light path to the receptors—the retinal blood vessels—are diverted away from the foveola. This central region of the fovea is therefore dependent on the underlying choroid and pigment epithelium for oxygenation and metabolic sustenance.

Cones and Color Vision

A special property of the cone system is color vision. Perceiving color allows humans (and many other animals) to discriminate objects on the basis of the distribution of the wavelengths of light that they reflect to the eye. While differences in luminance (i.e., overall light intensity) are often sufficient to distinguish objects, color adds another perceptual dimension that is especially useful when differences in luminance are subtle or nonexistent. Color obviously gives us a quite different way of perceiving and describing the world we live in.

Unlike rods, which contain a single photopigment, there are three types of cones that differ in the photopigment they contain. Each of these photopigments has a different sensitivity to light of different wavelengths, and for this reason are referred to as "blue," "green," and "red" or, more appropriately, short (S), medium (M), and long (L) wavelength cones—terms that more or less describe their spectral sensitivities (Figure 10.12). This nomenclature implies that individual cones provide color information for the wavelength of light that excites them best. In fact, individual cones, like rods, are entirely color blind in that their response is simply a reflection of the number of photons they capture, regardless of the wavelength of the photon (or, more properly, its vibrational energy). It is impossible, therefore, to determine whether the change in the membrane potential of a particular cone has arisen from exposure to many photons at wavelengths to which the receptor is relatively insensitive, or fewer photons at wavelengths to which it is most sensitive. This ambiguity can only be resolved by *comparing* the activity in different classes of cones. Based on the responses of individual ganglion cells, and cells at higher levels in the visual pathway (see Chapter 11), comparisons of this type are clearly involved in how the visual system extracts color information from spectral stimuli. Despite these insights, a full understanding of the neural mechanisms that underlie color perception has been elusive (Box D).

Much additional information about color vision has come from studies of individuals with abnormal color detecting abilities. Color vision deficiencies result either from the inherited failure to make one or more of the cone pigments or from an alteration in the absorption spectra of cone pigments (or, rarely, from lesions in the central stations that process color information; see Chapter 11). Under normal conditions, most people can match any color in a test stimulus by adjusting the intensity of three superimposed light sources generating long, medium, and short wavelengths. The fact that only three such sources are needed to match (nearly) all the perceived colors is strong

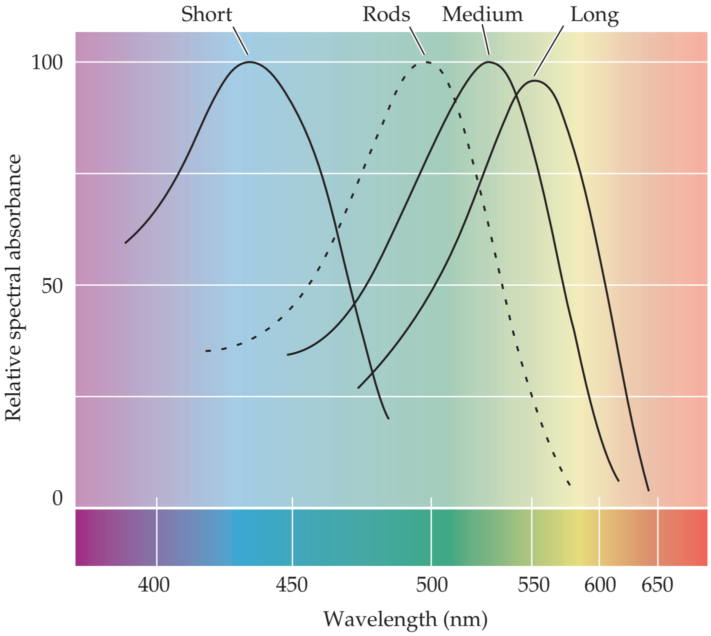

Figure 10.12 Color vision. The light absorption spectra of the four photopigments in the normal human retina. (Recall that light is defined as electromagnetic radiation having wavelengths between ~400 and 700 nm.) The solid curves indicate the three kinds of cone opsins; the dashed curve shows rod rhodopsin for comparison. Absorbance is defined as the log value of the intensity of incident light divided by intensity of transmitted light.

Box D

The Importance of Context in Color Perception

Seeing color logically demands that retinal responses to different wavelengths in some way be *compared*. The discovery of the three human cone types and their different absorption spectra is correctly regarded, therefore, as the basis for human color vision. Nevertheless, how these human cone types and the higher-order neurons they contact (see Chapter 11) produce the sensations of color is still unclear. Indeed, this issue has been debated by some of the greatest minds in science (Hering, Helmholtz, Maxwell, Schroedinger, and Mach, to name only a few) since Thomas Young first proposed that humans must have three different receptive "particles"—i.e., the three cone types.

A fundamental problem has been that, although the relative activities of three cone types can more or less explain the colors perceived in color-matching experiments performed in the laboratory, the perception of color is strongly influenced by context. For example, a patch returning the exact same spectrum of wavelengths to the eye can appear quite different depending on its surround, a phenomenon called *color contrast* (Figure A). Moreover, test patches returning different spectra to the eye can appear to be the same color, an effect called *color constancy* (Figure B). Although these phenomena were well known in the nineteenth century, they were not accorded a central place in color vision theory until Edwin Land's work in the 1950s. In his most famous demonstration, Land (who among other achievements founded the Polaroid company and became a billionaire) used a collage of colored papers that have been referred to as "the Land Mondrians" because of their similarity to the work of the Dutch artist Piet Mondrian.

Using a telemetric photometer and three adjustable illuminators generating short, middle, and long wavelength light, Land showed that two patches that in white light appeared quite different in color (e. g., green and brown) continued to look their respective colors even when the three illuminators were adjusted so that the light being returned from the "green" surfaces produced exactly the same readings on the three telephotometers as had previously come from the "brown" surface—a striking demonstration of color constancy.

The phenomena of color contrast and color constancy have led to a heated modern debate about how color percepts are generated that now spans several decades. For Land, the answer lay in a series of ratiometric equations that could integrate the spectral returns of different regions over the entire scene. It was recognized even before Land's death in 1991, however, that his so-called retinex theory did not work in all circumstances and was in any event a description rather than an explanation. An alternative explanation of these contextual aspects of color vision is that color, like brightness, is generated empirically according to what spectral stimuli have typically signified in past experience (see Box E).

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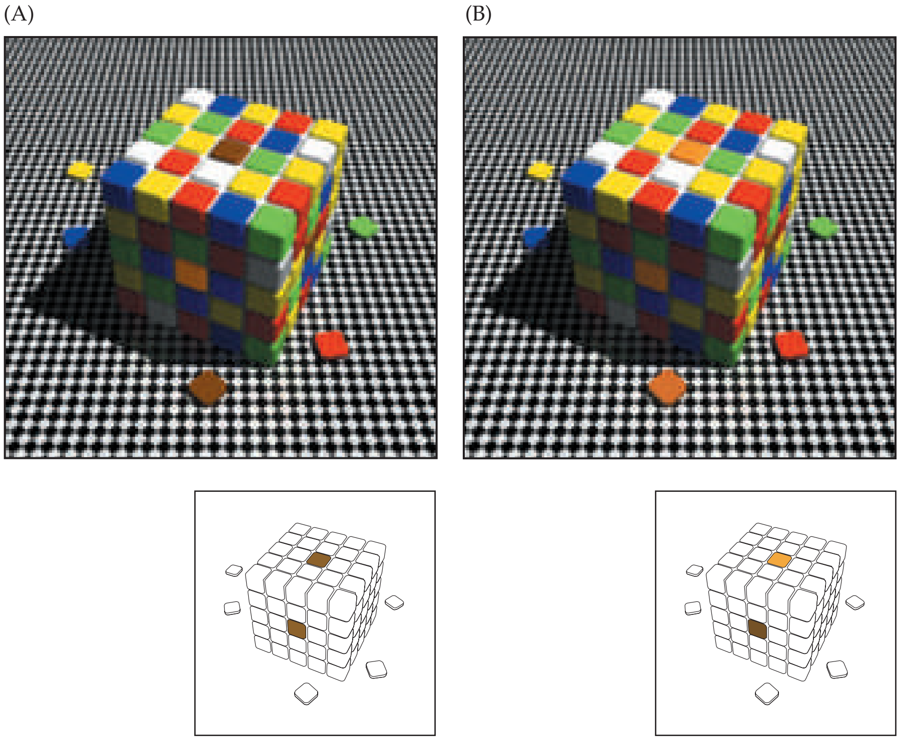


The genesis of contrast and constancy effects by exactly the same context. The two panels demonstrate the effects on apparent color when two *similarly* reflective target surfaces (A) or two *differently* reflective target surfaces (B) are presented in the *same* context in which all the information provided is consistent with illumination that differs only in intensity. The appearances of the relevant target surfaces in a neutral context are shown in the insets below. (From Purves and Lotto, 2003) confirmation of the fact that color sensation is based on the relative levels of activity in three sets of cones with different absorption spectra. That color vision is **trichromatic** was first recognized by Thomas Young at the beginning of the nineteenth century (thus, people with normal color vision are called *trichromats*). For about 5–6% of the male population in the United States and a much smaller percentage of the female population, however, color vision is more limited. Only two bandwidths of light are needed to match all the colors that these individuals can perceive; the third color category is simply not seen. Such **dichromacy**, or “color blindness” as it is commonly called, is inherited as a recessive, sex-linked characteristic and exists in two forms: *protanopia*, in which all color matches can be achieved by using only green and blue light, and *deuteranopia*, in which all matches can be achieved by using only blue and red light. In another major class of color deficiencies, all three light sources (i.e., short, medium, and long wavelengths) are needed to make all possible color matches, but the matches are made using values that are significantly different from those used by most individuals. Some of these *anomalous trichromats* require more red than normal to match other colors (protanomalous trichromats); others require more green than normal (deuteranomalous trichromats).

Jeremy Nathans and his colleagues at Johns Hopkins University have provided a deeper understanding of these color vision deficiencies by identifying and sequencing the genes that encode the three human cone pigments (Figure 10.13). The genes that encode the red and green pigments show a high degree of sequence homology and lie adjacent to each other on the X chromosome, thus explaining the prevalence of color blindness in males. In contrast, the blue-sensitive pigment gene is found on chromosome 7 and is quite different in its amino acid sequence. These facts suggest that the red and green pigment genes evolved relatively recently, perhaps as a result of the duplication of a single ancestral gene; they also explain why most color vision abnormalities involve the red and green cone pigments.

Human dichromats lack one of the three cone pigments, either because the corresponding gene is missing or because it exists as a hybrid of the red and green pigment genes (see Figure 10.13). For example, some dichromats lack the green pigment gene altogether, while others have a hybrid gene that is thought to produce a red-like pigment in the “green” cones. Anomalous trichromats also possess hybrid genes, but these genes elaborate pigments

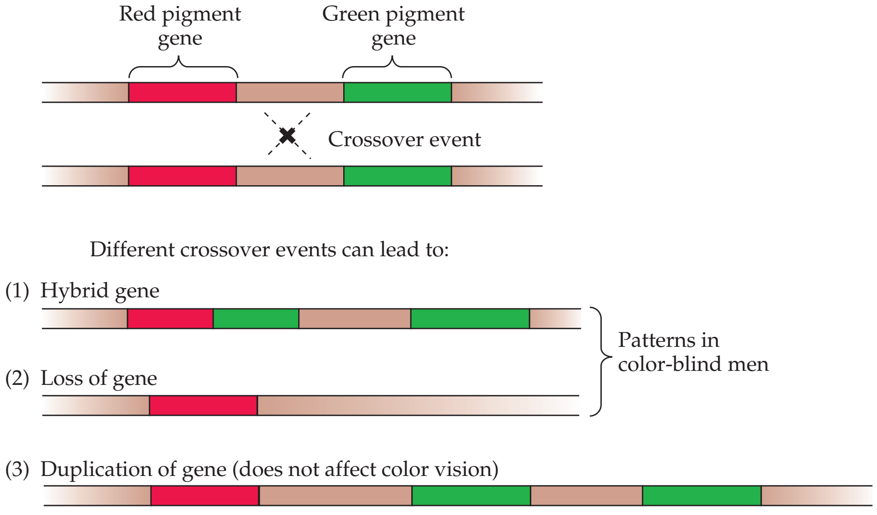

Red pigment gene
Green pigment gene
Crossover event
Different crossover events can lead to:
(1) Hybrid gene
(2) Loss of gene
Patterns in color-blind men
(3) Duplication of gene (does not affect color vision)

Figure 10.13 Many deficiencies of color vision are the result of genetic alterations in the red or green cone pigments due to the crossing over of chromosomes during meiosis. This recombination can lead to the loss of a gene, the duplication of a gene, or the formation of a hybrid with characteristics distinct from those of normal genes.

whose spectral properties lie between those of the normal red and green pigments. Thus, although most anomalous trichromats have distinct sets of medium and long-wavelength cones, there is more overlap in their absorption spectra than in normal trichromats, and thus less difference in how the two sets of cones respond to a given wavelength (with resulting anomalies in color perception).

Retinal Circuits for Detecting Luminance Change

Despite the esthetically pleasing nature of color vision, most of the information in visual scenes consists of spatial variations in light intensity (a black and white movie, for example, has most of the information a color version has, although it is deficient in some respects and usually is less fun to watch). How the spatial patterns of light and dark that fall on the photoreceptors are deciphered by central targets has been a vexing problem (Box E). To understand what is accomplished by the complex neural circuits within the retina during this process, it is useful to start by considering the responses of individual retinal ganglion cells to small spots of light. Stephen Kuffler, working at Johns Hopkins University in the 1950s, pioneered this approach by characterizing the responses of single ganglion cells in the cat retina. He found that each ganglion cell responds to stimulation of a small circular patch of the retina, which defines the cell's receptive field (see Chapter 8 for discussion of receptive fields). Based on these responses, Kuffler distinguished two classes of ganglion cells, "on"-center and "off"-center (Figure 10.14).

Turning on a spot of light in the receptive field center of an **on-center ganglion cell** produces a burst of action potentials. The same stimulus applied to the receptive field center of an **off-center ganglion cell** reduces the rate of

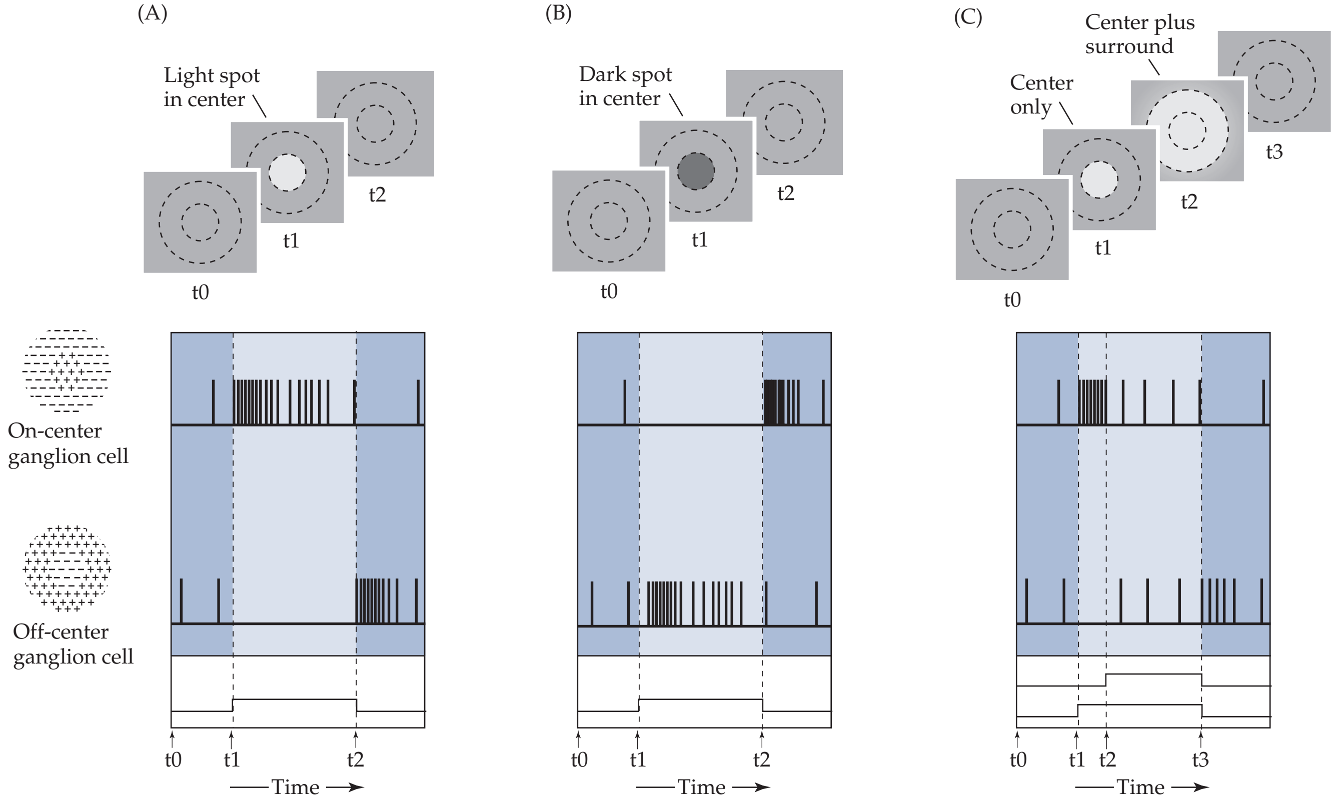


Figure 10.14 The responses of on-center and off-center retinal ganglion cells to stimulation of different regions of their receptive fields. Upper panels indicate the time sequence of stimulus changes. (A) Effects of light spot in the receptive field center. (B) Effects of dark spot in the receptive field center. (C) Effects of light spot in the center followed by the addition of light in the surround.

Box E

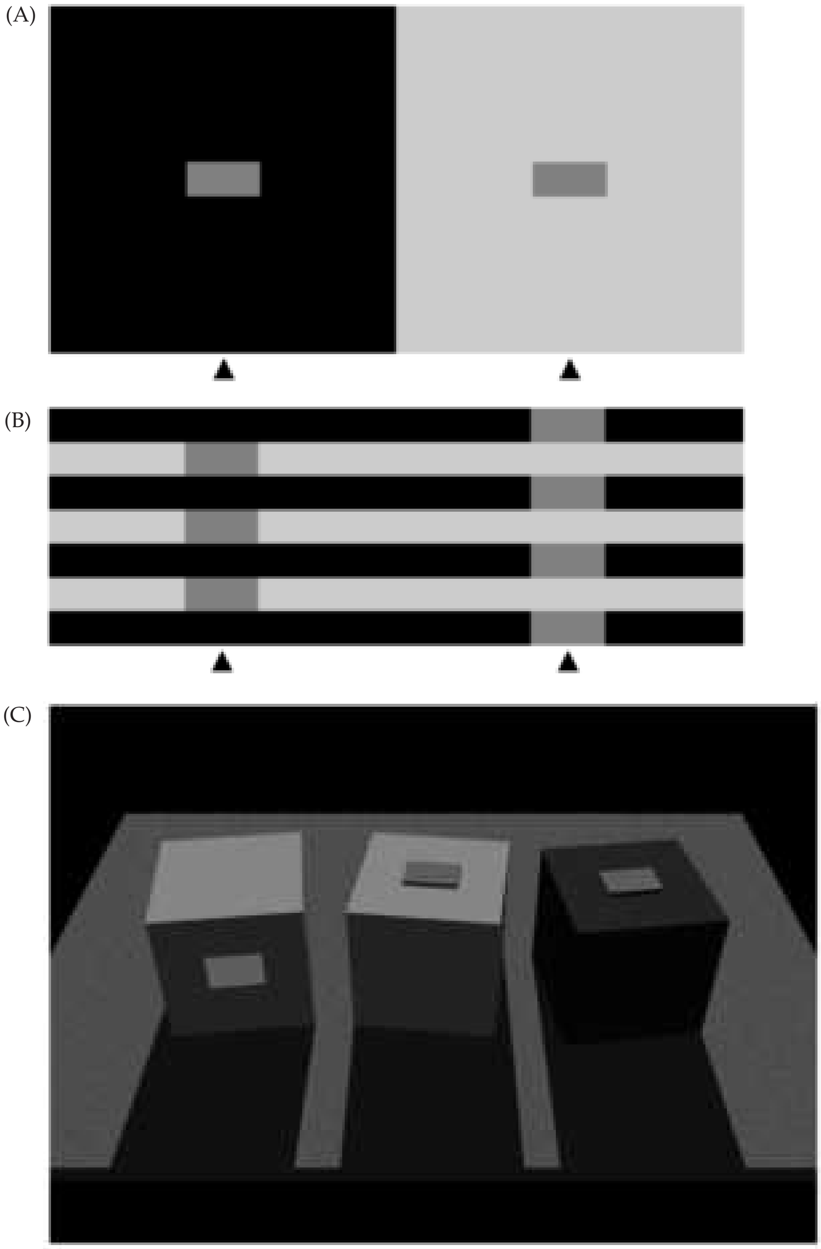
The Perception of Light Intensity

Understanding the link between retinal stimulation and what we see (perception) is arguably the central problem in vision, and the relation of luminance (a physical measurement of light intensity) and brightness (the sensation elicited by light intensity) is probably the simplest place to consider this challenge.

As indicated in the text, how we see the brightness differences (i.e., contrast) between adjacent territories with distinct luminances depends in the first instance on the relative firing rate of retinal ganglion cells, modified by lateral interactions. However, there is a problem with the assumption that the central nervous system simply "reads out" these relative rates of ganglion cell activity to sense brightness. The difficulty, as in perceiving color, is that the brightness of a given target is markedly affected by its context in ways that are difficult or impossible to explain in terms of the retinal output as such. The accompanying figures, which illustrate two simultaneous brightness contrast illusions, help make this point. In Figure A, two photometrically identical (equiluminant) gray squares appear differently bright as a function of the background in which they are presented.

A conventional interpretation of this phenomenon is that the receptive field properties illustrated in Figures 10.14 through 10.17 cause ganglion cells to fire differently depending on whether the surround of the equiluminant target is dark or light. The demonstration in Figure B, however, undermines this explanation, since in this case the target surrounded by more dark area actually looks *darker* than the same target surrounded by more light area.

An alternative interpretation of luminance perception that can account for these puzzling phenomena is that brightness percepts are generated on a statistical basis as a means of contending with the inherent ambiguity of luminance (i.e., the fact that a given value of luminance can be generated by many different combinations of illumination and surface reflectance properties). Since to be successful an observer has to respond to the real-world sources of luminance and not to light intensity as such, this ambiguity of the retinal stimulus presents a quandary. A plausible solution to



(A) Standard illusion of simultaneous brightness contrast. (B) Another illusion of simultaneous brightness contrast that is difficult to explain in conventional terms. (C) Cartoons of some possible sources of the standard simultaneous brightness contrast illusion in (A). (Courtesy of R. Beau Lotto and Dale Purves.)

the inherent uncertainty of the relationship between luminance values and their actual sources would be to generate the sensation of brightness elicited by a given luminance (e.g., in the brightness of the identical test patches in the figure) on the basis of what the luminance of the test patches had typically turned out to be in the past experience of human observers. To get the gist of this explanation consider Figure C, which illustrates the point that the two equiluminant target patches in Figure A could have been generated by two differently painted surfaces in different illuminants, as in a comparison of the target patches on the left and middle cubes, or two similarly reflecting surfaces in similar amounts of light, as in a comparison of the target patches on the middle and right cubes. An expedient—and perhaps the only—way the visual system can cope with this ambiguity is to generate the perception of the stimulus in Figure A (and in Figure B) empirically, i.e., based on what the target patches typically turned out to signify in the past. Since the equiluminant targets will have arisen from a variety of possible sources, it makes sense to have the brightness elicited by the patches determined statistically by the relative frequency of occurrence of that luminance in the particular context in which it is presented. The advantage of seeing luminance according to the relative probabilities of the possible sources of the stimulus is that percepts generated in this way give the observer the best chance of making appropriate behavioral responses to profoundly ambiguous stimuli.

References

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discharge, and when the spot of light is turned off, the cell responds with a burst of action potentials (Figure 10.14A). Complementary patterns of activity are found for each cell type when a dark spot is placed in the receptive field center (Figure 10.14B). Thus, on-center cells increase their discharge rate to luminance *increments* in the receptive field center, whereas off-center cells increase their discharge rate to luminance *decrements* in the receptive field center.

On- and off-center ganglion cells are present in roughly equal numbers. The receptive fields have overlapping distributions, so that every point on the retinal surface (that is, every part of visual space) is analyzed by several on-center and several off-center ganglion cells. A rationale for having these two distinct types of retinal ganglion cells was suggested by Peter Schiller and his colleagues at the Massachusetts Institute of Technology, who examined the effects of pharmacologically inactivating on-center ganglion cells on a monkey's ability to detect a variety of visual stimuli. After silencing on-center ganglion cells, the animals showed a deficit in their ability to detect stimuli that were brighter than the background; however, they could still see objects that were darker than the background.

These observations imply that information about increases or decreases in luminance is carried separately to the brain by the axons of these two different types of retinal ganglion cells. Having separate luminance "channels" means that changes in light intensity, whether increases or decreases, are always conveyed to the brain by an increased number of action potentials. Because ganglion cells rapidly adapt to changes in luminance, their "resting" discharge rate in constant illumination is relatively low. Although an increase in discharge rate above resting level serves as a reliable signal, a decrease in firing rate from an initially low rate of discharge might not. Thus, having luminance changes signaled by two classes of adaptable cells provides unambiguous information about both luminance increments and decrements.

The functional differences between these two ganglion cell types can be understood in terms of both their anatomy and their physiological properties and relationships (Figure 10.15). On- and off-center ganglion cells have dendrites that arborize in separate strata of the inner plexiform layer, forming synapses selectively with the terminals of on- and off-center bipolar cells that respond to luminance increases and decreases, respectively (Figure 10.15A). As mentioned previously, the principal difference between ganglion cells and bipolar cells lies in the nature of their electrical response. Like most other cells in the retina, bipolar cells have graded potentials rather than action potentials. Graded depolarization of bipolar cells leads to an increase in transmitter release (glutamate) at their synapses and consequent depolarization of the on-center ganglion cells that they contact via AMPA, kainate, and NMDA receptors.

The selective response of on- and off-center bipolar cells to light increments and decrements is explained by the fact that they express different types of glutamate receptors (Figure 10.15A). Off-center bipolar cells have ionotropic receptors (AMPA and kainate) that cause the cells to depolarize in response to glutamate released from photoreceptor terminals. In contrast, on-center bipolar cells express a G-protein-coupled metabotropic glutamate receptor (mGluR6). When bound to glutamate, these receptors activate an intracellular cascade that closes cGMP-gated Na^+ channels, reducing inward

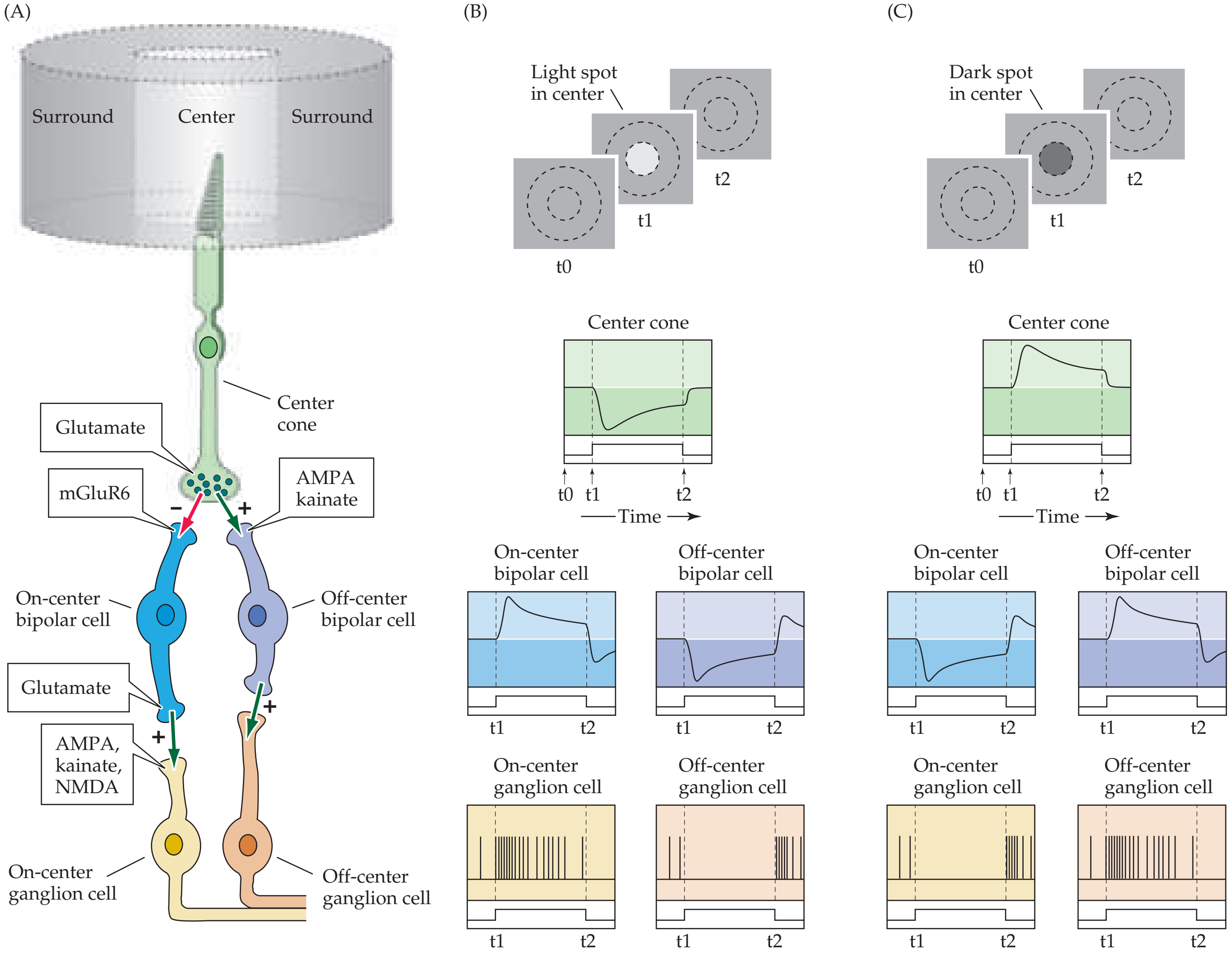
(A)
Surround
Center
Surround
Glutamate
Center cone
mGluR6
AMPA kainate
−
+
On-center bipolar cell
Off-center bipolar cell
Glutamate
+
+
AMPA, kainate, NMDA
On-center ganglion cell
Off-center ganglion cell
(B)
Light spot in center
t0
t1
t2
Center cone
t0 t1 t2
Time
On-center bipolar cell
Off-center bipolar cell
t1 t2
On-center ganglion cell
Off-center ganglion cell
t1 t2
(C)
Dark spot in center
t0
t1
t2
Center cone
t0 t1 t2
Time
On-center bipolar cell
Off-center bipolar cell
t1 t2
On-center ganglion cell
Off-center ganglion cell
t1 t2

Figure 10.15 Circuitry responsible for generating receptive field center responses of retinal ganglion cells. (A) Functional anatomy of cone inputs to the center of a ganglion cell receptive field. A plus indicates a sign-conserving synapse; a minus represents a sign-inverting synapse. (B) Responses of various cell types to the presentation of a light spot in the center of the ganglion cell receptive field. (C) Responses of various cell types to the presentation of a dark spot in the center of the ganglion cell receptive field.

current and hyperpolarizing the cell. Thus, glutamate has opposite effects on these two classes of cells, depolarizing off-center bipolar cells and hyperpolarizing on-center cells. Photoreceptor synapses with off-center bipolar cells are called sign-conserving, since the sign of the change in membrane potential of the bipolar cell (depolarization or hyperpolarization) is the same as that in the photoreceptor (Figure 10.15B,C). Photoreceptor synapses with on-center bipolar cells are called sign-inverting because the change in the membrane potential of the bipolar cell is the opposite of that in the photoreceptor.

In order to understand the response of on- and off-center bipolar cells to changes in light intensity, recall that photoreceptors hyperpolarize in response to light increments, decreasing their release of neurotransmitter (Figure 10.15B). Under these conditions, on-center bipolar cells contacted by the photoreceptors are freed from the hyperpolarizing influence of the photoreceptor's transmitter, and they depolarize. In contrast, for off-center cells, the reduction in glutamate represents the withdrawal of a depolarizing influence, and these cells hyperpolarize. Decrements in light intensity naturally have the opposite effect on these two classes of bipolar cells, hyperpolarizing on-center cells and depolarizing off-center ones (Figure 10.15C).

Kuffler's work also called attention to the fact that retinal ganglion cells do not act as simple photodetectors. Indeed, most ganglion cells are relatively poor at signaling differences in the level of diffuse illumination. Instead, they are sensitive to *differences* between the level of illumination that falls on the receptive field center and the level of illumination that falls on the surround—that is, to **luminance contrast**. The center of a ganglion cell receptive field is surrounded by a concentric region that, when stimulated, antagonizes the response to stimulation of the receptive field center (see Figure 10.14C). For example, as a spot of light is moved from the center of the receptive field of an on-center cell toward its periphery, the response of the cell to the spot of light decreases (Figure 10.16). When the spot falls completely outside the center (that is, in the surround), the response of the cell falls below its resting level; the cell is effectively inhibited until the distance from the center is so great that the spot no longer falls on the receptive field at all, in which case the cell returns to its resting level of firing. Off-center

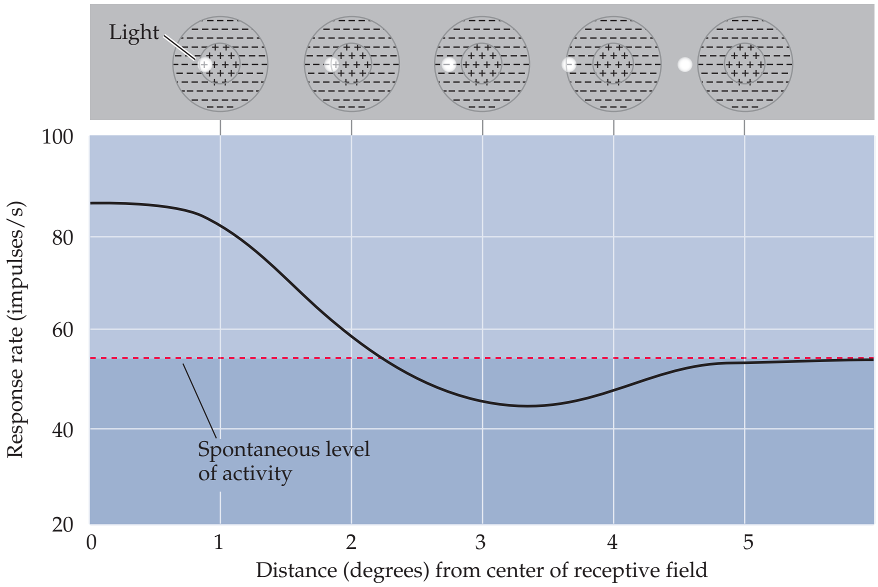

Figure 10.16 Rate of discharge of an on-center ganglion cell to a spot of light as a function of the distance of the spot from the receptive field center. Zero on the x axis corresponds to the center; at a distance of 5°, the spot falls outside the receptive field.

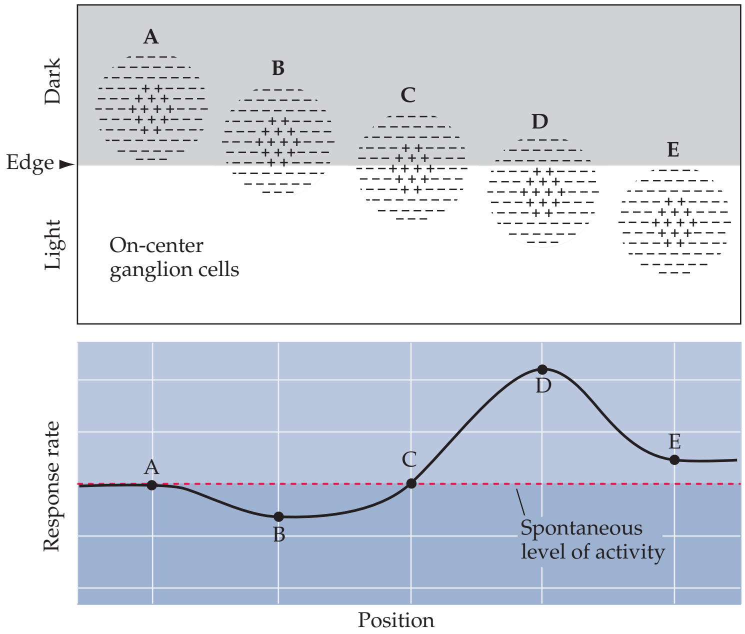

Figure 10.17 Responses of a hypothetical population of on-center ganglion cells whose receptive fields (A–E) are distributed across a light-dark edge. Those cells whose activity is most affected have receptive fields that lie along the light-dark edge.

cells exhibit a similar surround antagonism. Stimulation of the surround by light opposes the decrease in firing rate that occurs when the center is stimulated alone, and reduces the response to light decrements in the center (compare Figures 10.14A and 10.14C).

Because of their antagonistic surrounds, ganglion cells respond much more vigorously to small spots of light confined to their receptive field centers than to large spots, or to uniform illumination of the visual field (see Figure 10.14C).

To appreciate how center-surround antagonism makes the ganglion cell sensitive to luminance contrast, consider the activity levels in a hypothetical population of on-center ganglion cells whose receptive fields are distributed across a retinal image of a light-dark edge (Figure 10.17). The neurons whose firing rates are most affected by this stimulus—either increased (neuron D) or decreased (neuron B)—are those with receptive fields that lie along the light-dark border; those with receptive fields completely illuminated (or completely darkened) are less affected (neurons A and E). Thus, the information supplied by the retina to central visual stations for further processing does not give equal weight to all regions of the visual scene; rather, it emphasizes the regions where there are differences in luminance.

Contribution of Retinal Circuits to Light Adaptation

In addition to making ganglion cells especially sensitive to light-dark borders in the visual scene, center-surround mechanisms make a significant contribution to the process of **light adaptation**. As illustrated for an on-center cell in Figure 10.18, the response rate of a ganglion cell to a small spot of light turned on in its receptive field center varies as a function of the spot's intensity. In fact, response rate is proportional to the spot's intensity over a range of about one log unit. However, the intensity of spot illumination required to evoke a given discharge rate is dependent on the background level of illumination. Increases in background level of illumination are accompanied by adaptive shifts in the cell's operating range such that

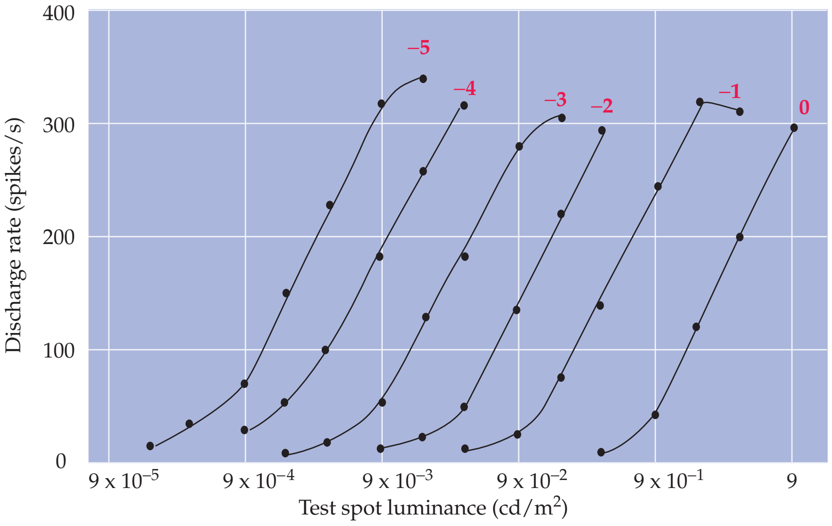

Figure 10.18 A series of curves illustrating the discharge rate of a single on-center ganglion cell to the onset of a small test spot of light in the center of its receptive field. Each curve represents the discharge rate evoked by spots of varying intensity at a constant background level of illumination, which is given by the red numbers at the top of each curve (the highest background level is 0, the lowest –5). The response rate is proportional to stimulus intensity over a range of 1 log unit, but the operating range shifts to the right as the background level of illumination increases.

greater stimulus intensities are required to achieve the same discharge rate. Thus, firing rate is not an absolute measure of light intensity, but rather signals the difference from background level of illumination.

Because the range of light intensities over which we can see is enormous compared to the narrow range of ganglion cell discharge rates (see Figure 10.9), adaptational mechanisms are essential. By scaling the ganglion cell's response to ambient levels of illumination, the entire dynamic range of a neuron's firing rate is used to encode information about intensity differences over the range of luminance values that are relevant for a given visual scene. Due to the antagonistic center-surround organization of retinal ganglion cells, the signal sent to the brain from the retina downplays the background level of illumination (see Figure 10.14). This arrangement presumably explains why the relative brightness of objects remains much the same over a wide range of lighting conditions. In bright sunlight, for example, the print on this page reflects considerably more light to the eye than it does in room light. In fact, the *print* reflects more light in sunlight than the *paper* reflects in room light; yet it continues to look black and the page white, indoors or out.

Like the mechanism responsible for generating the on- and off-center response, the antagonistic surround of ganglion cells is a product of interactions that occur at the early stages of retinal processing (Figure 10.19). Much of the antagonism is thought to arise via lateral connections established by horizontal cells and receptor terminals. Horizontal cells receive synaptic inputs from photoreceptor terminals and are linked via gap junctions with a vast network of other horizontal cells distributed over a wide area of the retinal surface. As a result, the activity in horizontal cells reflects levels of illumination over a broad area of the retina. Although the details of their actions are not entirely clear, horizontal cells are thought to exert their influence via the release of neurotransmitter directly onto photoreceptor terminals, regulating the amount of transmitter that the photoreceptors release onto bipolar cell dendrites.

Glutamate release from photoreceptor terminals has a depolarizing effect on horizontal cells (sign-conserving synapse), while the transmitter released from horizontal cells (GABA) has a hyperpolarizing influence on photoreceptor terminals (sign-inverting synapse) (Figure 10.19A). As a result, the net effect of inputs from the horizontal cell network is to oppose changes in the

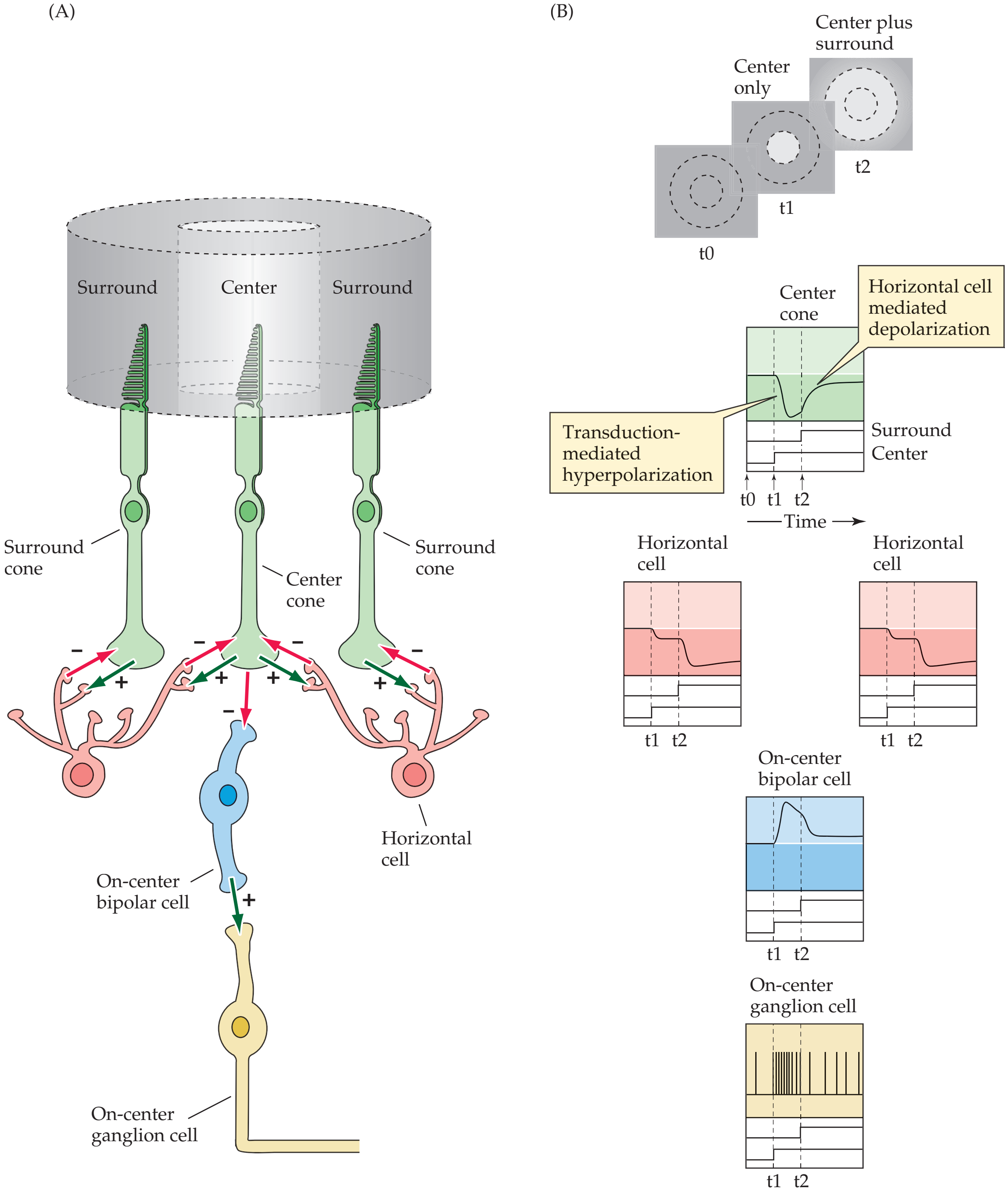
(A)
(B)
Surround
Center
Surround
Surround cone
Center cone
Surround cone
–
+
–
+
+
–
–
+
–
+
Horizontal cell
On-center bipolar cell
On-center ganglion cell
Center plus surround
Center only
t0
t1
t2
Center cone
Horizontal cell mediated depolarization
Transduction-mediated hyperpolarization
Surround
Center
t0 t1 t2
Time
Horizontal cell
Horizontal cell
t1 t2
t1 t2
On-center bipolar cell
t1 t2
On-center ganglion cell
t1 t2

Figure 10.19 Circuitry responsible for generating the receptive field surround of an on-center retinal ganglion cell. (A) Functional anatomy of horizontal cell inputs responsible for surround antagonism. A plus indicates a sign-conserving synapse; a minus represents a sign-inverting synapse. (B) Responses of various cell types to the presentation of a light spot in the center of the receptive field (t1) followed by the addition of light stimulation in the surround (t2). Light stimulation of the surround leads to hyperpolarization of the horizontal cells and a decrease in the release of inhibitory transmitter (GABA) onto the photoreceptor terminals. The net effect is to depolarize the center cone terminal, offsetting much of the hyperpolarization induced by the transduction cascade in the center cone's outer segment.

membrane potential of the photoreceptor that are induced by phototransduction events in the outer segment. How these events lead to surround suppression in an on-center ganglion cell is illustrated in Figure 10.19. A small spot of light centered on a photoreceptor supplying input to the center of the ganglion cell's receptive field produces a strong hyperpolarizing response in the photoreceptor. Under these conditions, changes in the membrane potential of the horizontal cells that synapse with the photoreceptor terminal are relatively small, and the response of the photoreceptor to light is largely determined by its phototransduction cascade (Figure10.19B). With the addition of light to the surround, however, the impact of the horizontal network becomes significantly greater; the light-induced reduction in the release of glutamate from the photoreceptors in the surround leads to a strong hyperpolarization of the horizontal cells whose processes converge on the terminal of the photoreceptor in the receptive field center. The reduction in GABA release from the horizontal cells has a depolarizing effect on the membrane potential of the central photoreceptor, reducing the light-evoked response and ultimately reducing the firing rate of the on-center ganglion cell.

Thus, even at the earliest stages in visual processing, neural signals do not represent the absolute numbers of photons that are captured by receptors, but rather the relative intensity of stimulation—how much the current level of stimulation differs from ambient levels. While it may seem that the actions of horizontal cells decrease the sensitivity of the retina, they play a critical role in allowing the full range of the photoreceptor's electrical response (about 30 mV) to be applied to the limited range of stimulus intensities that are present at any given moment. The network mechanisms of adaptation described here function in conjunction with cellular mechanisms in the receptor outer segments that regulate the sensitivity of the phototransduction cascade at different light levels. Together, they allow retinal circuits to convey the most salient aspects of luminance changes to the central stages of the visual system described in the following chapter.

Summary

The light that falls on photoreceptors is transformed by retinal circuitry into a pattern of action potentials that ganglion cell axons convey to the visual centers in the brain. This process begins with phototransduction, a biochemical cascade that ultimately regulates the opening and closing of ion channels in the membrane of the photoreceptor's outer segment, and thereby the amount of neurotransmitter the photoreceptor releases. Two systems of photoreceptors—rods and cones—allow the visual system to meet the conflicting demands of sensitivity and acuity, respectively. Retinal ganglion cells operate quite differently from the photoreceptor cells. The center-surround arrangement of ganglion cell receptive fields makes these neurons particularly sensitive to luminance contrast and relatively insensitive to the overall level of illumination. It also allows the retina to adapt, such that it can respond effectively over the enormous range of illuminant intensities in the world. The underlying organization is generated by the synaptic interactions between photoreceptors, horizontal cells, and bipolar cells in the outer plexiform layer. As a result, the signal sent to the visual centers in the brain is already highly processed when it leaves the retina, emphasizing those aspects of the visual scene that convey the most information.

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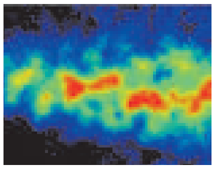
Chapter 11



Central Visual Pathways

Overview

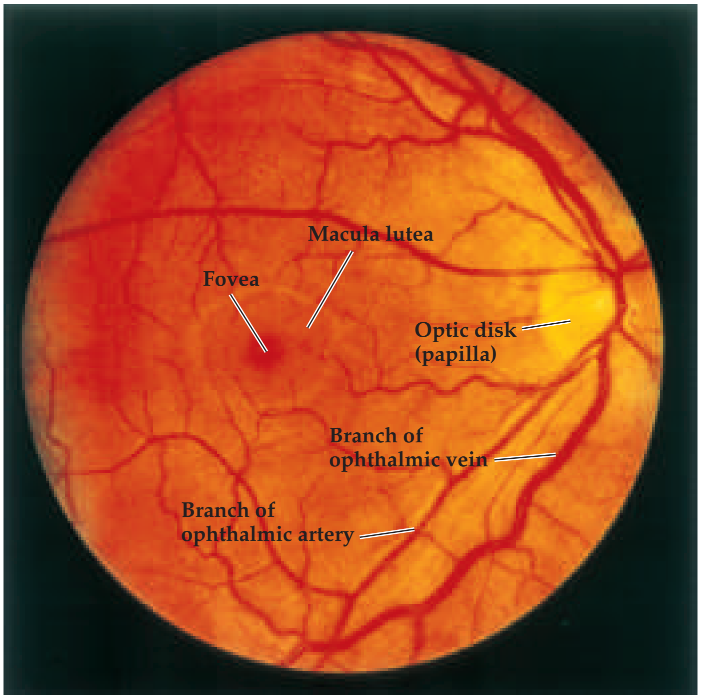
Information supplied by the retina initiates interactions between multiple subdivisions of the brain that eventually lead to conscious perception of the visual scene, at the same time stimulating more conventional reflexes such as adjusting the size of the pupil, directing the eyes to targets of interest, and regulating homeostatic behaviors that are tied to the day/night cycle. The pathways and structures that mediate this broad range of functions are necessarily diverse. Of these, the primary visual pathway from the retina to the dorsal lateral geniculate nucleus in the thalamus and on to the primary visual cortex is the most important and certainly the most thoroughly studied component of the visual system. Different classes of neurons within this pathway encode the varieties of visual information—luminance, spectral differences, orientation, and motion—that we ultimately see. The parallel processing of different categories of visual information continues in cortical pathways that extend beyond primary visual cortex, supplying a variety of visual areas in the occipital, parietal, and temporal lobes. Visual areas in the temporal lobe are primarily involved in object recognition, whereas those in the parietal lobe are concerned with motion. Normal vision depends on the integration of information in all these cortical areas. The processes underlying visual perception are not understood and remain one of the central challenges of modern neuroscience.

Central Projections of Retinal Ganglion Cells

Ganglion cell axons exit the retina through a circular region in its nasal part called the **optic disk** (or optic papilla), where they bundle together to form the **optic nerve**. This region of the retina contains no photoreceptors and, because it is insensitive to light, produces the perceptual phenomenon known as the **blind spot** (Box A). The optic disk is easily identified as a whitish circular area when the retina is examined with an ophthalmoscope; it also is recognized as the site from which the ophthalmic artery and veins enter (or leave) the eye (Figure 11.1). In addition to being a conspicuous retinal landmark, the appearance of the optic disk is a useful gauge of intracranial pressure. The subarachnoid space surrounding the optic nerve is continuous with that of the brain; as a result, increases in intracranial pressure—a sign of serious neurological problems such as a space-occupying lesion—can be detected as *papilledema*, a swelling of the optic disk.

Axons in the optic nerve run a straight course to the **optic chiasm** at the base of the diencephalon. In humans, about 60% of these fibers cross in the chiasm, while the other 40% continue toward the thalamus and midbrain targets on the same side. Once past the chiasm, the ganglion cell axons on each

Figure 11.1 The retinal surface of the left eye, viewed with an ophthalmoscope. The optic disk is the region where the ganglion cell axons leave the retina to form the optic nerve; it is also characterized by the entrance and exit, respectively, of the ophthalmic arteries and veins that supply the retina. The macula lutea can be seen as a distinct area at the center of the optical axis (the optic disk lies nasally); the macula is the region of the retina that has the highest visual acuity. The fovea is a depression or pit about 1.5 mm in diameter that lies at the center of the macula (see Chapter 10).



side form the **optic tract**. Thus, the optic tract, unlike the optic nerve, contains fibers from *both* eyes. The partial crossing (or decussation) of ganglion cell axons at the optic chiasm allows information from corresponding points on the two retinas to be processed by approximately the same cortical site in each hemisphere, an important issue that is considered in the next section.

The ganglion cell axons in the optic tract reach a number of structures in the diencephalon and midbrain (Figure 11.2). The major target in the diencephalon is the **dorsal lateral geniculate nucleus** of the thalamus. Neurons in the lateral geniculate nucleus, like their counterparts in the thalamic relays of other sensory systems, send their axons to the cerebral cortex via the internal capsule. These axons pass through a portion of the internal capsule called the **optic radiation** and terminate in the **primary visual cortex**, or **striate cortex** (also referred to as **Brodmann's area 17** or **V1**), which lies largely along and within the calcarine fissure in the occipital lobe. The **retinogeniculostriate pathway**, or **primary visual pathway**, conveys information that is essential for most of what is thought of as seeing. Thus, damage anywhere along this route results in serious visual impairment.

A second major target of the ganglion cell axons is a collection of neurons that lies between the thalamus and the midbrain in a region known as the **pretectum**. Although small in size compared to the lateral geniculate nucleus, the pretectum is particularly important as the coordinating center for the **pupillary light reflex** (i.e., the reduction in the diameter of the pupil that occurs when sufficient light falls on the retina) (Figure 11.3). The initial component of the pupillary light reflex pathway is a bilateral projection from the retina to the pretectum. Pretectal neurons, in turn, project to the **Edinger-Westphal nucleus**, a small group of nerve cells that lies close to the nucleus of the oculomotor nerve (cranial nerve III) in the midbrain. The Edinger-Westphal nucleus contains the preganglionic parasympathetic neurons that send their axons via the oculomotor nerve to terminate on neurons in the ciliary

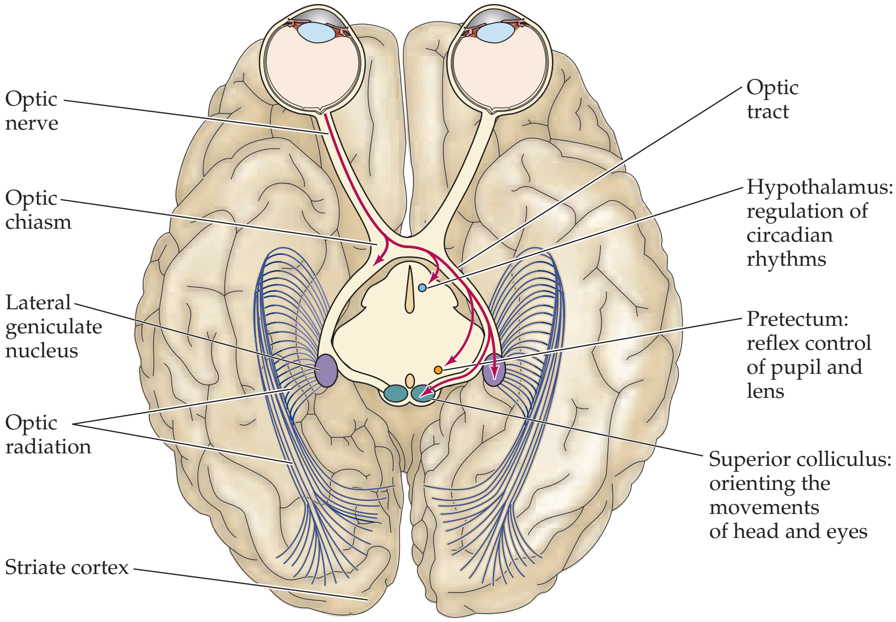
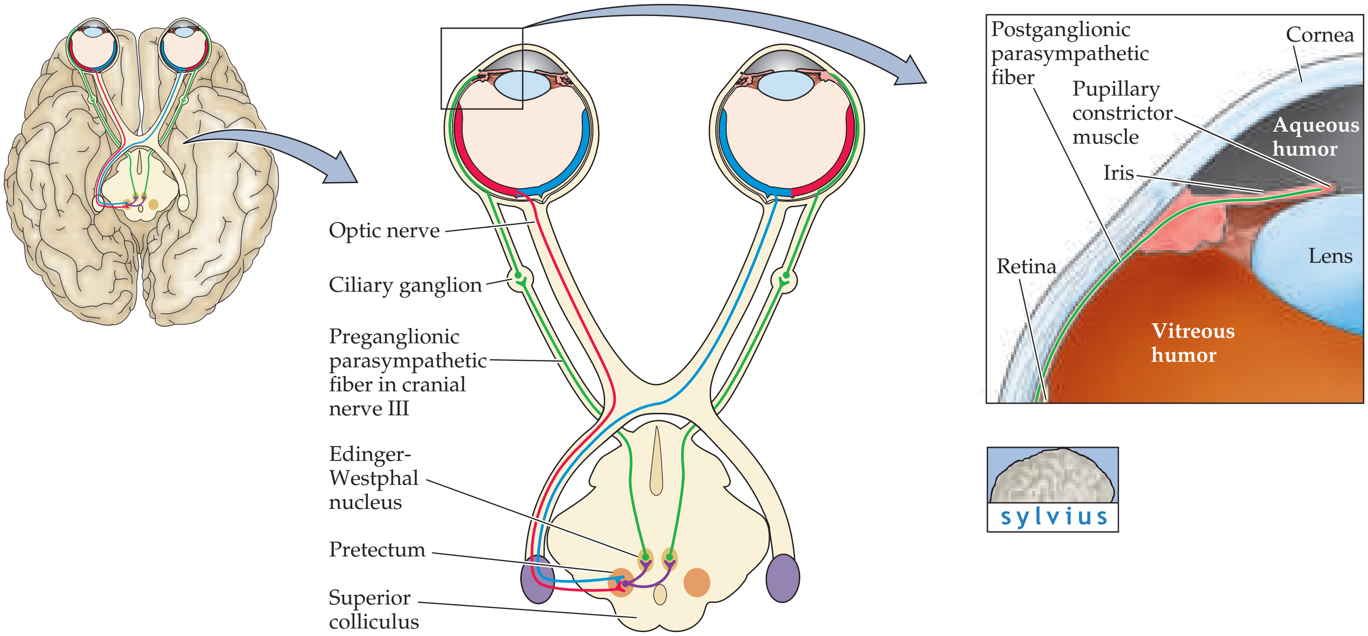

Optic nerve
Optic chiasm
Lateral geniculate nucleus
Optic radiation
Striate cortex
Optic tract
Hypothalamus: regulation of circadian rhythms
Pretectum: reflex control of pupil and lens
Superior colliculus: orienting the movements of head and eyes

Figure 11.2 Central projections of retinal ganglion cells. Ganglion cell axons terminate in the lateral geniculate nucleus of the thalamus, the superior colliculus, the pretectum, and the hypothalamus. For clarity, only the crossing axons of the right eye are shown (view is looking up at the inferior surface of the brain).

ganglion (see Chapter 19). Neurons in the ciliary ganglion innervate the constrictor muscle in the iris, which decreases the diameter of the pupil when activated. Shining light in the eye thus leads to an increase in the activity of pretectal neurons, which stimulates the Edinger-Westphal neurons and the ciliary ganglion neurons they innervate, thus constricting the pupil.

In addition to its normal role in regulating the amount of light that enters the eye, the pupillary reflex provides an important diagnostic tool that allows the physician to test the integrity of the visual sensory apparatus, the motor outflow to the pupillary muscles, and the central pathways that medi-

Figure 11.3 The circuitry responsible for the pupillary light reflex. This pathway includes bilateral projections from the retina to the pretectum and projections from the pretectum to the Edinger-Westphal nucleus. Neurons in the Edinger-Westphal nucleus terminate in the ciliary ganglion, and neurons in the ciliary ganglion innervate the pupillary constrictor muscles. Notice that the afferent axons activate both Edinger-Westphal nuclei via the neurons in the pretectum.


Optic nerve
Ciliary ganglion
Preganglionic parasympathetic fiber in cranial nerve III
Edinger-Westphal nucleus
Pretectum
Superior colliculus
Postganglionic parasympathetic fiber
Pupillary constrictor muscle
Iris
Retina
Cornea
Aqueous humor
Lens
Vitreous humor

Box A

The Blind Spot

It is logical to suppose that a visual field defect (called a *scotoma*) arising from damage to the retina or central visual pathways would be obvious to the individual suffering from such pathology. When the deficit involves a peripheral region of the visual field, however, a scotoma often goes unnoticed until a car accident or some other mishap all too dramatically reveals the sensory loss. In fact, all of us have a physiological scotoma of which we are quite unaware, the so-called "blind spot." The blind spot is the substantial gap in each monocular visual field that corresponds to the location of the optic disk, the receptor-free region of the retina where the optic nerve leaves the eye (see Figure 11.1).

To find the "blind spot" of the right eye, close the left eye and fixate on the X shown in the figure here, holding the book about 30–40 centimeters away. Now take a pencil in your right hand and, without breaking fixation, move the tip slowly toward the X from the right side of the page. At some point, the tip of the pencil (indeed the whole end of the pencil) will disappear; mark this point and continue to move the pencil to the left until it reappears; then make another mark. The borders of the blind spot along the vertical axis can be determined in the same way by moving the pencil up and down so that its path falls between the two horizontal marks. To prove that information from the region of visual space bounded by the marks is really not perceived, put a penny inside the demarcated area. When you fixate the X with both eyes and then close the left eye, the penny will disappear, a seemingly magical event that amazed the French royal court when it was first reported by the natural philosopher Edmé Mariotte in 1668.

How can we be unaware of such a large defect in the visual field (typically about 5°–8°)? The optic disk is located in the nasal retina of each eye. With both eyes open, information about the corresponding region of visual space is, of course, available from the temporal retina of the other eye. But this fact does not explain why the blind spot remains undetected with one eye closed. When the world is viewed monocularly, the visual system appears to "fill-in" the missing part of the scene based on the information supplied by the regions surrounding the optic disk. To observe this phenomenon, notice what happens when a pencil or some other object lies *across* the optic disk representation. Remarkably, the pencil looks complete! Although electrophysiological recordings have shown that neurons in the visual cortex whose receptive fields lie in the optic disk representation can be activated by stimulating the regions that surround the optic disk of the contralateral eye, suggesting that "filling-in" the blind spot is based on cortical mechanisms that integrate information from different points in the visual field, the mechanism of this striking phenomenon is not clear. Herman von Helmholtz pointed out in the nineteenth century that it may just be that this part of the visual world is ignored, the pencil being completed across the blind spot because the rest of the scene simply "collapses" around it.

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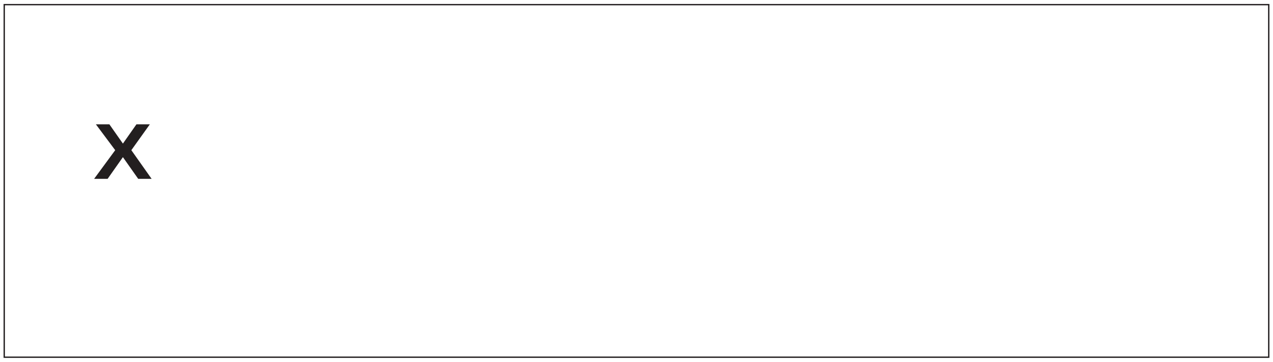


ate the reflex. Under normal conditions, the pupils of both eyes respond identically, regardless of which eye is stimulated; that is, light in one eye produces constriction of both the stimulated eye (the direct response) and the unstimulated eye (the consensual response; see Figure 11.3). Comparing the response in the two eyes is often helpful in localizing a lesion. For example, a direct response in the left eye without a consensual response in the right eye suggests a problem with the visceral motor outflow to the right eye, possibly as a result of damage to the oculomotor nerve or Edinger-Westphal nucleus in the brainstem. Failure to elicit a response (either direct or indirect) to stimulation of the left eye if both eyes respond normally to stimulation of the right eye suggests damage to the sensory input from the left eye, possibly to the left retina or optic nerve.

There are several other important targets of retinal ganglion cell axons. One is the **suprachiasmatic nucleus** of the hypothalamus, a small group of neurons at the base of the diencephalon (see Box A in Chapter 20). The **retinohypothalamic pathway** is the route by which variation in light levels influences the broad spectrum of visceral functions that are entrained to the day/night cycle (see Chapters 20 and 27). Another target is the **superior colliculus**, a prominent structure visible on the dorsal surface of the midbrain (see Figure 1.14). The superior colliculus coordinates head and eye movements to visual (as well as other) targets; its functions are considered in Chapter 19.

The type of visual information required to perform the functions of these different retinal targets is quite different. Reading the text on this page, for example, requires a high-resolution sampling of the retinal image, whereas regulating circadian rhythms and adjusting the pupil accordingly require only a measure of overall changes in light levels, and little or no information about the features of the image. It should come as no surprise, then, that there is a diversity of ganglion cell types that provide information appropriate to the functions of these different targets.

Projections to the lateral geniculate nucleus (which are described in more detail later) arise from at least three broad classes of ganglion cells, whose tuning properties are appropriate for mediating the richness of visual perception (high acuity, color, motion). In contrast, projections to the hypothalamus and the pretectum arise from ganglion cells that lack these properties and are highly suited for detecting luminance flux. The retinal specializations responsible for constructing these distinct classes of retinal ganglion cells are only beginning to be identified; they include not only differences in ganglion cell synaptic connections, but in the locus of the phototransduction event itself. Unlike the majority of ganglion cells, which depend on rods and cones for their sensitivity to light, the ganglion cells that project to the hypothalamus and pretectum express their own light-sensitive photopigment (*melanopsin*) and are capable of modulating their response to changes in light levels in the absence of signals from rods and cones. The presence of light sensitivity within this class of ganglion cells presumably explains why normal circadian rhythms are maintained in animals that have completely lost form vision due to degeneration of rod and cone photoreceptors.

The Retinotopic Representation of the Visual Field

The spatial relationships among the ganglion cells in the retina are maintained in most of their central targets as orderly representations or "maps" of visual space. Most of these structures receive information from both eyes, requiring that these inputs be integrated to form a coherent map of individ-

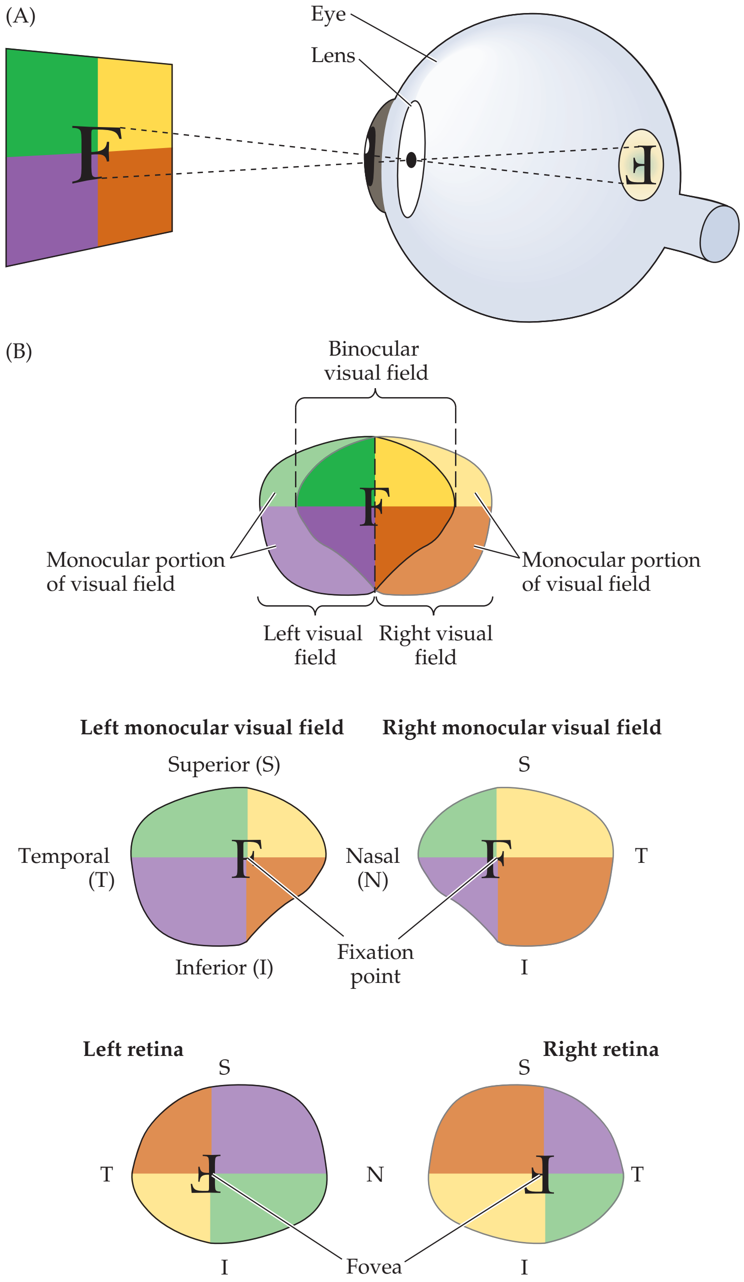

(A)
Eye
Lens
F
(B)
Binocular visual field
F
Monocular portion of visual field
Monocular portion of visual field
Left visual field
Right visual field
Left monocular visual field
Right monocular visual field
Superior (S)
S
Temporal (T)
Nasal (N)
T
F
F
Fixation point
Inferior (I)
I
Left retina
Right retina
S
S
T
N
T
Fovea
I
I

Figure 11.4 Projection of the visual fields onto the left and right retinas. (A) Projection of an image onto the surface of the retina. The passage of light rays through the pupil of the eye results in images that are inverted and left–right reversed on the retinal surface. (B) Retinal quadrants and their relation to the organization of monocular and binocular visual fields, as viewed from the back surface of the eyes. Vertical and horizontal lines drawn through the center of the fovea define retinal quadrants (bottom). Comparable lines drawn through the point of fixation define visual field quadrants (center). Color coding illustrates corresponding retinal and visual field quadrants. The overlap of the two monocular visual fields is shown at the top.

ual points in space. As a general rule, information from the left half of the visual world, whether it originates from the left or right eye, is represented in the right half of the brain, and vice versa.

Understanding the neural basis for the appropriate arrangement of inputs from the two eyes requires considering how images are projected onto the two retinas, and the central destination of the ganglion cells located in different parts of the retina. Each eye sees a part of visual space that defines its **visual field** (Figure 11.4A). For descriptive purposes, each retina and its corresponding visual field are divided into quadrants. In this scheme, the surface of the retina is subdivided by vertical and horizontal lines that intersect at the center of the fovea (Figure 11.4B). The vertical line divides the retina into **nasal** and **temporal divisions** and the horizontal line divides the retina into **superior** and **inferior divisions**. Corresponding vertical and horizontal lines in visual space (also called meridians) intersect at the **point of fixation** (the point in visual space that falls on the fovea) and define the quadrants of the visual field. The crossing of light rays diverging from different points on an object at the pupil causes the images of objects in the visual field to be inverted and left-right reversed on the retinal surface. As a result, objects in the temporal part of the visual field are seen by the nasal part of the retina, and objects in the superior part of the visual field are seen by the inferior part of the retina. (It may help in understanding Figure 11.4B to imagine that you are looking at the back surfaces of the retinas, with the corresponding visual fields projected onto them.)

With both eyes open, the two foveas are normally aligned on a single target in visual space, causing the visual fields of both eyes to overlap extensively (see Figure 11.4B and Figure 11.5). This **binocular field** of view consists of two symmetrical visual hemifields (left and right). The left binocular hemifield includes the nasal visual field of the right eye and the temporal visual field of the left eye; the right hemifield includes the temporal visual field of

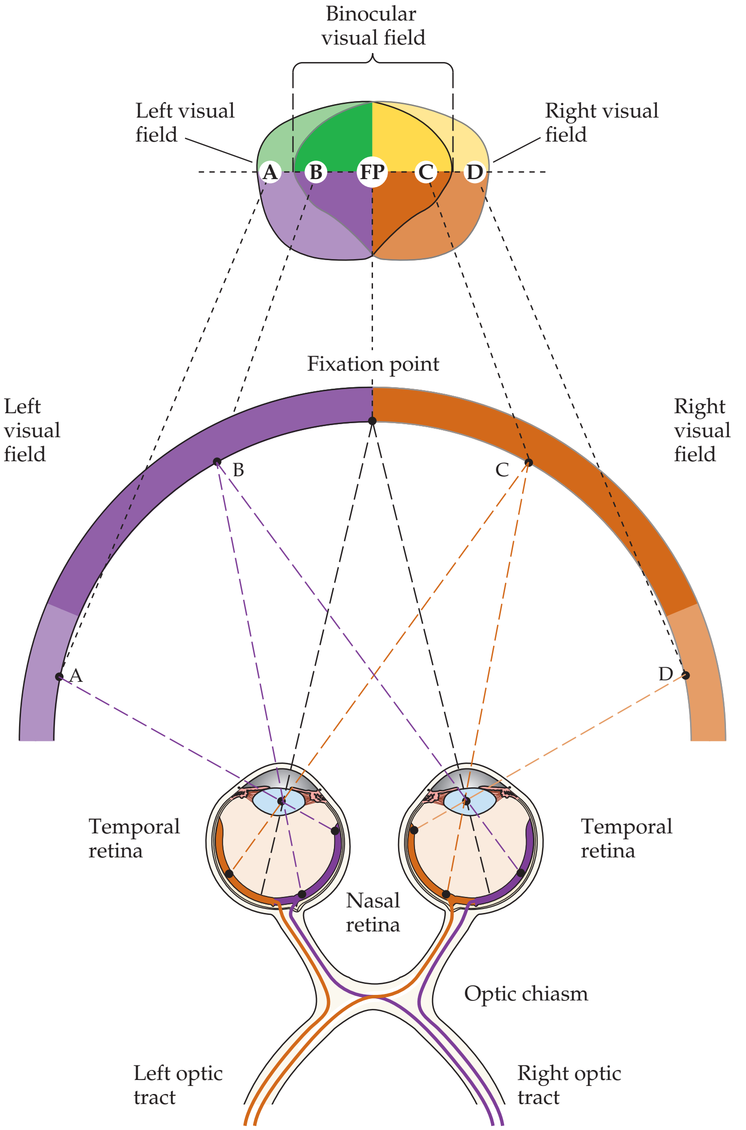


Figure 11.5 Projection of the binocular field of view onto the two retinas and its relation to the crossing of fibers in the optic chiasm. Points in the binocular portion of the left visual field (B) fall on the nasal retina of the left eye and the temporal retina of the right eye. Points in the binocular portion of the right visual field (C) fall on the nasal retina of the right eye and the temporal retina of the left eye. Points that lie in the monocular portions of the left and right visual fields (A and D) fall on the left and right nasal retinas, respectively. The axons of ganglion cells in the nasal retina cross in the optic chiasm, whereas those from the temporal retina do not. As a result, information from the left visual field is carried in the right optic tract, and information from the right visual field is carried in the left optic tract.

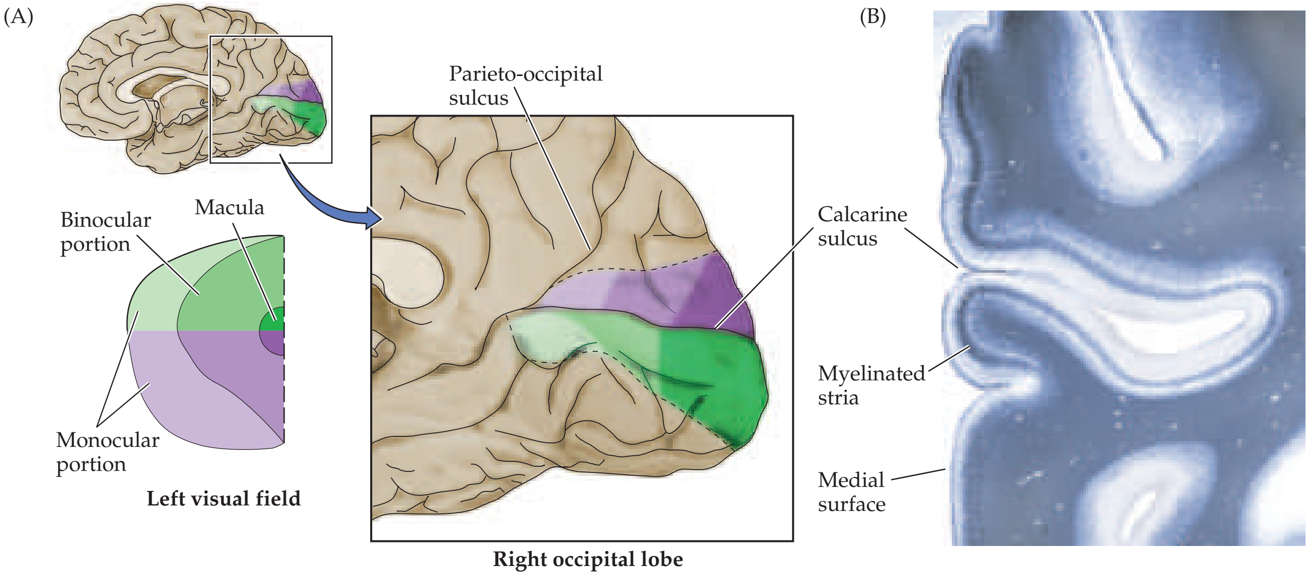
the right eye and the nasal visual field of the left eye. The temporal visual fields are more extensive than the nasal visual fields, reflecting the size of the nasal and temporal retinas respectively. As a result, vision in the periphery of the field of view is strictly monocular, mediated by the most medial portion of the nasal retina. Most of the rest of the field of view can be seen by both eyes; i.e., individual points in visual space lie in the nasal visual field of one eye and the temporal visual field of the other. It is worth noting, however, that the shape of the face and nose impact the extent of this region of binocular vision. In particular, the inferior nasal visual fields are less extensive than the superior nasal fields, and consequently the binocular field of view is smaller in the lower visual field than in the upper (see Figure 11.4B).

Ganglion cells that lie in the nasal division of each retina give rise to axons that cross in the chiasm, while those that lie in the temporal retina give rise to axons that remain on the same side (see Figure 11.5). The boundary (or line of decussation) between contralaterally and ipsilaterally projecting ganglion cells runs through the center of the fovea and defines the border between the nasal and temporal hemiretinas. Images of objects in the left visual hemifield (such as point B in Figure 11.5) fall on the nasal retina of the left eye and the temporal retina of the right eye, and the axons from ganglion cells in these regions of the two retinas project through the right optic tract. Objects in the right visual hemifield (such as point C in Figure 11.5) fall on the nasal retina of the right eye and the temporal retina of the left eye; the axons from ganglion cells in these regions project through the left optic tract. As mentioned previously, objects in the monocular portions of the visual hemifields (points A and D in Figure 11.5) are seen only by the most peripheral nasal retina of each eye; the axons of ganglion cells in these regions (like the rest of the nasal retina) run in the contralateral optic tract. Thus, unlike the optic nerve, the optic tract contains the axons of ganglion cells that originate in both eyes and represent the contralateral field of view.

Optic tract axons terminate in an orderly fashion within their target structures thus generating well ordered maps of the contralateral hemifield. For the primary visual pathway, the map of the contralateral hemifield that is established in the lateral geniculate nucleus is maintained in the projections of the lateral geniculate nucleus to the striate cortex (Figure 11.6). Thus the

sylvius

Figure 11.6 Visuotopic organization of the striate cortex in the right occipital lobe, as seen in mid-sagittal view. (A) The primary visual cortex occupies a large part of the occipital lobe. The area of central vision (the fovea) is represented over a disproportionately large part of the caudal portion of the lobe, whereas peripheral vision is represented more anteriorly. The upper visual field is represented below the calcarine sulcus, the lower field above the calcarine sulcus. (B) Photomicrograph of a coronal section of the human striate cortex, showing the characteristic myelinated band, or stria, that gives this region of the cortex its name. The calcarine sulcus on the medial surface of the occipital lobe is indicated. (B courtesy of T. Andrews and D. Purves.)



fovea is represented in the posterior part of the striate cortex, whereas the more peripheral regions of the retina are represented in progressively more anterior parts of the striate cortex. The upper visual field is mapped below the calcarine sulcus, and the lower visual field above it. As in the somatic sensory system, the amount of cortical area devoted to each unit area of the sensory surface is not uniform, but reflects the density of receptors and sensory axons that supply the peripheral region. Like the representation of the hand region in the somatic sensory cortex, the representation of the macula is therefore disproportionately large, occupying most of the caudal pole of the occipital lobe.

Visual Field Deficits

A variety of retinal or more central pathologies that involve the primary visual pathway can cause visual field deficits that are limited to particular regions of visual space. Because the spatial relationships in the retinas are maintained in central visual structures, a careful analysis of the visual fields can often indicate the site of neurological damage. Relatively large visual field deficits are called **anopsias** and smaller ones are called **scotomas** (see Box A). The former term is combined with various prefixes to indicate the specific region of the visual field from which sight has been lost (Figures 11.7 and 11.8).

Damage to the retina or one of the optic nerves before it reaches the chiasm results in a loss of vision that is limited to the eye of origin. In contrast, damage in the region of the optic chiasm—or more centrally—results in specific types of deficits that involve the visual fields of both eyes (Figure 11.8). Damage to structures that are central to the optic chiasm, including the optic tract, lateral geniculate nucleus, optic radiation, and visual cortex, results in deficits that are limited to the contralateral visual hemifield. For example, interruption of the optic tract on the right results in a loss of sight in the left visual field (that is, blindness in the temporal visual field of the left eye and the nasal visual field of the right eye). Because such damage affects corresponding parts of the visual field in each eye, there is a complete loss of vision in the affected region of the binocular visual field, and the deficit is referred to as a **homonymous hemianopsia** (in this case, a left homonymous hemianopsia).

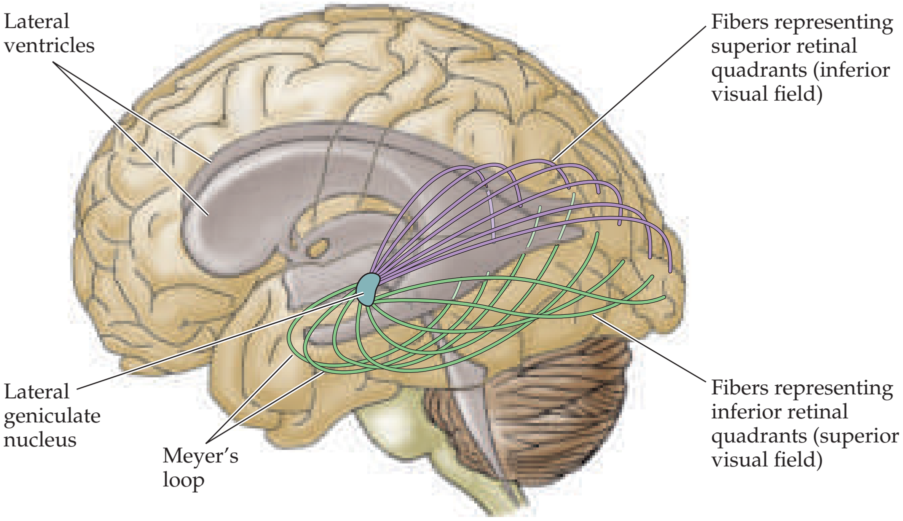

Lateral ventricles
Fibers representing superior retinal quadrants (inferior visual field)
Lateral geniculate nucleus
Meyer's loop
Fibers representing inferior retinal quadrants (superior visual field)

Figure 11.7 Course of the optic radiation to the striate cortex. Axons carrying information about the superior portion of the visual field sweep around the lateral horn of the ventricle in the temporal lobe (Meyer's loop) before reaching the occipital lobe. Those carrying information about the inferior portion of the visual field travel in the parietal lobe.

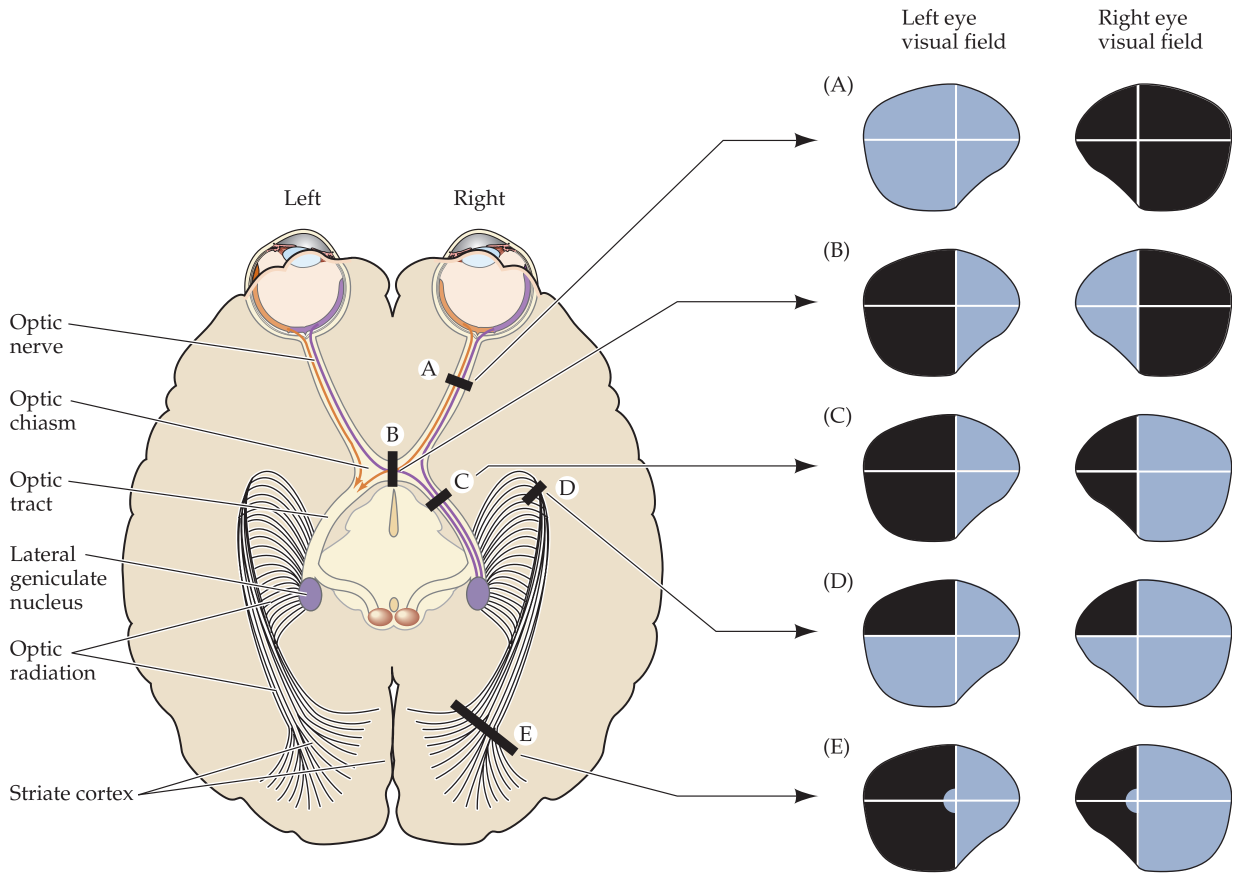


Figure 11.8 Visual field deficits resulting from damage at different points along the primary visual pathway. The diagram on the left illustrates the basic organization of the primary visual pathway and indicates the location of various lesions. The right panels illustrate the visual field deficits associated with each lesion. (A) Loss of vision in right eye. (B) Bitemporal (heteronomous) hemianopsia. (C) Left homonymous hemianopsia. (D) Left superior quadrantanopsia. (E) Left homonymous hemianopsia with macular sparing.

sylvius

In contrast, damage to the optic chiasm results in visual field deficits that involve noncorresponding parts of the visual field of each eye. For example, damage to the middle portion of the optic chiasm (which is often the result of pituitary tumors) can affect the fibers that are crossing from the nasal retina of each eye, leaving the uncrossed fibers from the temporal retinas intact. The resulting loss of vision is confined to the temporal visual field of each eye and is known as **bitemporal hemianopsia**. It is also called **heteronomous hemianopsia** to emphasize that the parts of the visual field that are lost in each eye do not overlap. Individuals with this condition are able to see in both left and right visual fields, provided both eyes are open. However, all information from the most peripheral parts of visual fields (which are seen only by the nasal retinas) is lost.

Damage to central visual structures is rarely complete. As a result, the deficits associated with damage to the chiasm, optic tract, optic radiation, or visual cortex are typically more limited than those shown in Figure 11.8. This is especially true for damage along the optic radiation, which fans out under the temporal and parietal lobes in its course from the lateral geniculate nucleus to the striate cortex. Some of the optic radiation axons run out into the temporal lobe on their route to the striate cortex, a branch called **Meyer's loop** (see Figure 11.7). Meyer's loop carries information from the superior portion of the contralateral visual field. More medial parts of the optic radiation, which pass under the cortex of the parietal lobe, carry information from the inferior portion of the contralateral visual field. Damage to parts of the temporal lobe with involvement of Meyer's loop can thus result in a superior

homonymous quadrantanopsia; damage to the optic radiation underlying the parietal cortex results in an inferior homonymous quadrantanopsia.

Injury to central visual structures can also lead to a phenomenon called *macular sparing*, i.e., the loss of vision throughout wide areas of the visual field, with the exception of foveal vision. Macular sparing is commonly found with damage to the cortex, but can be a feature of damage anywhere along the length of the visual pathway. Although several explanations for macular sparing have been offered, including overlap in the pattern of crossed and uncrossed ganglion cells supplying central vision, the basis for this selective preservation is not clear.

The Functional Organization of the Striate Cortex

Much in the same way that Stephen Kuffler explored the response properties of individual retinal ganglion cells (see Chapter 10), David Hubel and Torsten Wiesel used microelectrode recordings to examine the properties of neurons in more central visual structures.

The responses of neurons in the lateral geniculate nucleus were found to be remarkably similar to those in the retina, with a center-surround receptive field organization and selectivity for luminance increases or decreases. However, the small spots of light that were so effective at stimulating neurons in the retina and lateral geniculate nucleus were largely ineffective in visual cortex. Instead, most cortical neurons in cats and monkeys responded vigorously to light–dark bars or edges, and only if the bars were presented at a particular range of orientations within the cell's receptive field (Figure 11.9). The responses of cortical neurons are thus tuned to the orientation of edges, much like cone receptors are tuned to the wavelength of light; the peak in the tuning curve (the orientation to which a cell is most responsive) is referred to as the neuron's preferred orientation. By sampling the responses of a large number of single cells, Hubel and Weisel demonstrated that all edge orientations were roughly equally represented in visual cortex. As a

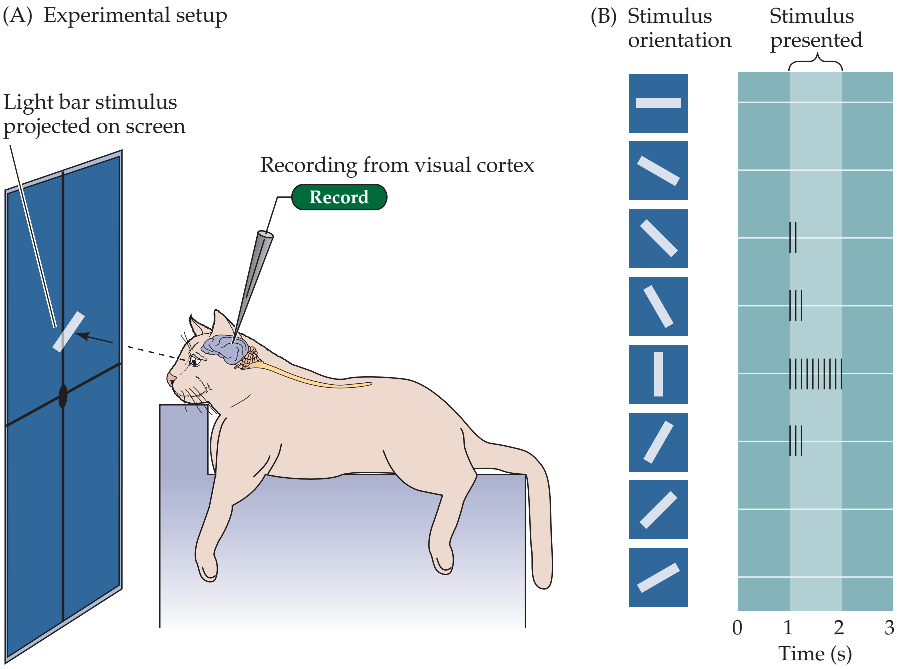


Figure 11.9 Neurons in the primary visual cortex respond selectively to oriented edges. (A) An anesthetized animal is fitted with contact lenses to focus the eyes on a screen, where images can be projected; an extracellular electrode records the neuronal responses. (B) Neurons in the primary visual cortex typically respond vigorously to a bar of light oriented at a particular angle and weakly—or not at all—to other orientations.

result, a given orientation in a visual scene appears to be "encoded" in the activity of a distinct population of **orientation-selective neurons**.

Hubel and Wiesel also found that there are subtly different subtypes within a class of neurons that preferred the same orientation. For example, the receptive fields of some cortical cells, which they called **simple cells**, were composed of spatially separate "on" and "off" response zones, as if the "on" and "off" centers of lateral geniculate cells that supplied these neurons were arrayed in separate parallel bands. Other neurons, referred to as **complex cells**, exhibited mixed "on" and "off" responses throughout their receptive field, as if they received their inputs from a number of simple cells. Further analysis uncovered cortical neurons sensitive to the *length* of the bar of light that was moved across their receptive field, decreasing their rate of response when the bar exceeded a certain length. Still other cells responded selectively to the *direction* in which an edge moved across their receptive field. Although the mechanisms responsible for generating these selective responses are still not well understood, there is little doubt that the specificity of the receptive field properties of neurons in the striate cortex (and beyond) plays an important role in determining the basic attributes of visual scenes.

Another feature that distinguishes the responses of neurons in the striate cortex from those at earlier stages in the primary visual pathway is **binocularity**. Although the lateral geniculate nucleus receives inputs from both eyes, the axons terminate in separate layers, so that individual geniculate

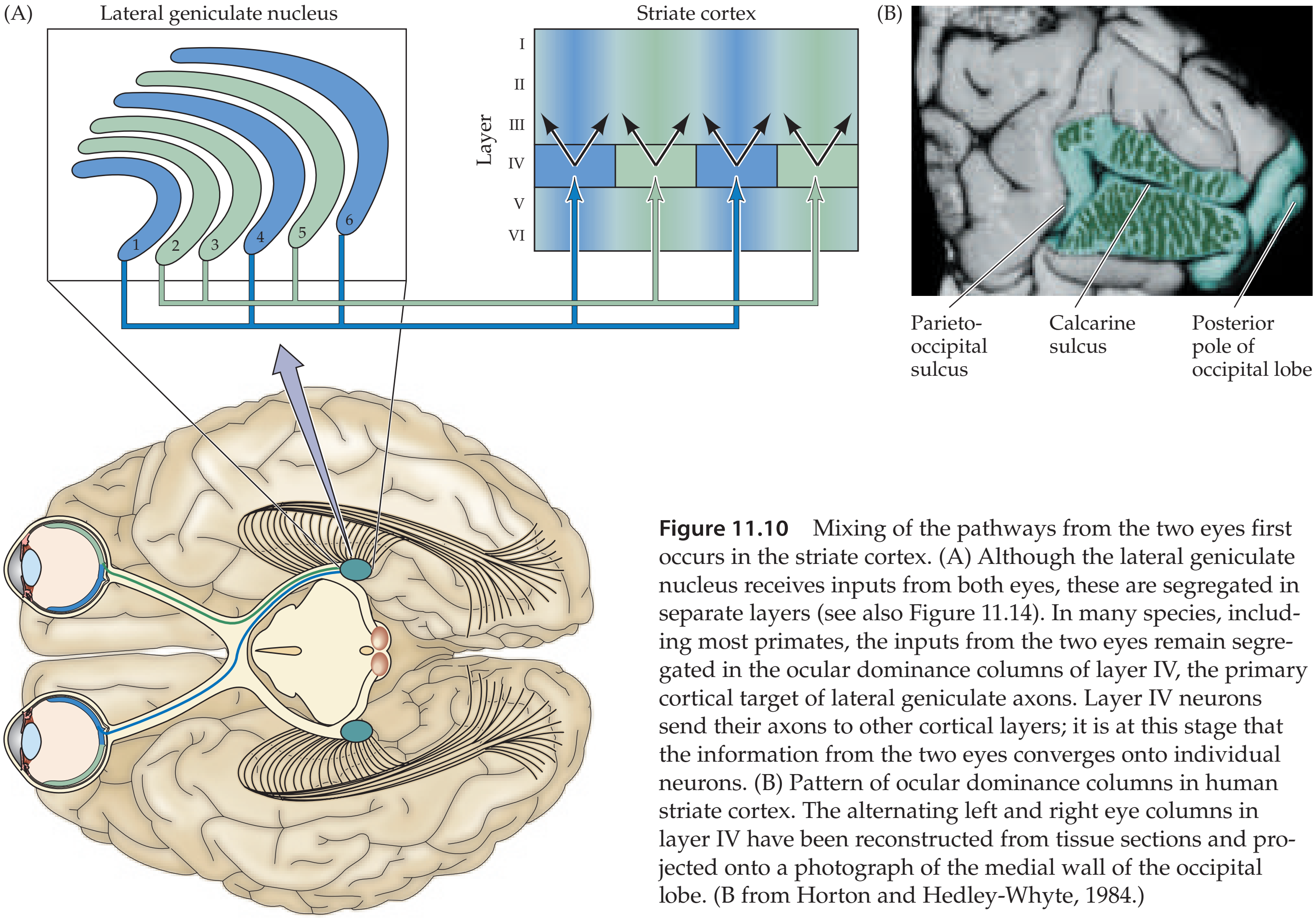


Figure 11.10 Mixing of the pathways from the two eyes first occurs in the striate cortex. (A) Although the lateral geniculate nucleus receives inputs from both eyes, these are segregated in separate layers (see also Figure 11.14). In many species, including most primates, the inputs from the two eyes remain segregated in the ocular dominance columns of layer IV, the primary cortical target of lateral geniculate axons. Layer IV neurons send their axons to other cortical layers; it is at this stage that the information from the two eyes converges onto individual neurons. (B) Pattern of ocular dominance columns in human striate cortex. The alternating left and right eye columns in layer IV have been reconstructed from tissue sections and projected onto a photograph of the medial wall of the occipital lobe. (B from Horton and Hedley-Whyte, 1984.)

neurons are monocular, driven by either the left or right eye but not by both (Figure 11.10; see also Figure 11.14). In some species, including most (but not all) primates, inputs from the left and right eyes remain segregated to some degree even beyond the geniculate because the axons of geniculate neurons terminate in alternating eye-specific columns within cortical layer IV—the so-called **ocular dominance columns** (see the next section). Beyond this point, the signals from the two eyes are combined at the cellular level. Thus, most cortical neurons have binocular receptive fields, and these fields are almost identical, having the same size, shape, preferred orientation, and roughly the same position in the visual field of each eye.

Bringing together the inputs from the two eyes at the level of the striate cortex provides a basis for **stereopsis**, the special sensation of depth that arises from viewing nearby objects with two eyes instead of one. Because the two eyes look at the world from slightly different angles, objects that lie in front of or behind the plane of fixation project to noncorresponding points on the two retinas. To convince yourself of this fact, hold your hand at arm's length and fixate on the tip of one finger. Maintain fixation on the finger as you hold a pencil in your other hand about half as far away. At this distance, the image of the pencil falls on noncorresponding points on the two retinas and will therefore be perceived as two separate pencils (a phenomenon called double vision, or *diplopia*). If the pencil is now moved toward the finger (the point of fixation), the two images of the pencil fuse and a single pencil is seen in front of the finger. Thus, for a small distance on either side of the plane of fixation, where the disparity between the two views of the world remains modest, a single image is perceived; the disparity between the two eye views of objects nearer or farther than the point of fixation is interpreted as depth (Figure 11.11).

Although the neurophysiological basis of stereopsis is not understood, some neurons in the striate cortex and in other visual cortical areas have receptive field properties that make them good candidates for extracting information about binocular disparity. Unlike many binocular cells whose monocular receptive fields sample the same region of visual space, these neurons have monocular fields that are slightly displaced (or perhaps differ in their internal organization) so that the cell is maximally activated by stimuli that fall on noncorresponding parts of the retinas. Some of these neurons (so-called **far cells**) discharge to disparities beyond the plane of fixation, while others (**near cells**) respond to disparities in front of the plane of fixation. The pattern of activity in these different classes of neurons seems likely to contribute to sensations of stereoscopic depth (Box B).

Interestingly, the preservation of the binocular responses of cortical neurons is contingent on the normal activity from the two eyes during early postnatal life. Anything that creates an imbalance in the activity of the two eyes—for example, the clouding of one lens or the abnormal alignment of the eyes during infancy (strabismus)—can permanently reduce the effectiveness of one eye in driving cortical neurons, and thus impair the ability to use binocular information as a cue for depth. Early detection and correction of visual problems is therefore essential for normal visual function in maturity (see Chapter 23).

The Columnar Organization of the Striate Cortex

The variety of response properties exhibited by cortical neurons raises the question of how neurons with different receptive fields are arranged within striate cortex. For the most part, the responses of neurons are qualitatively

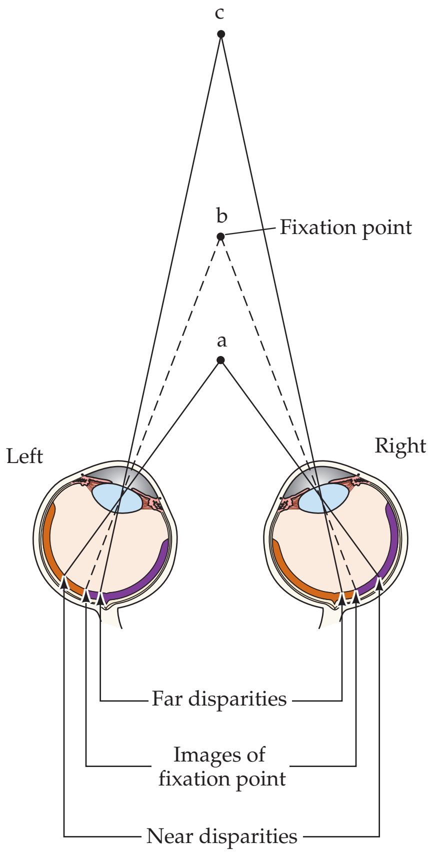


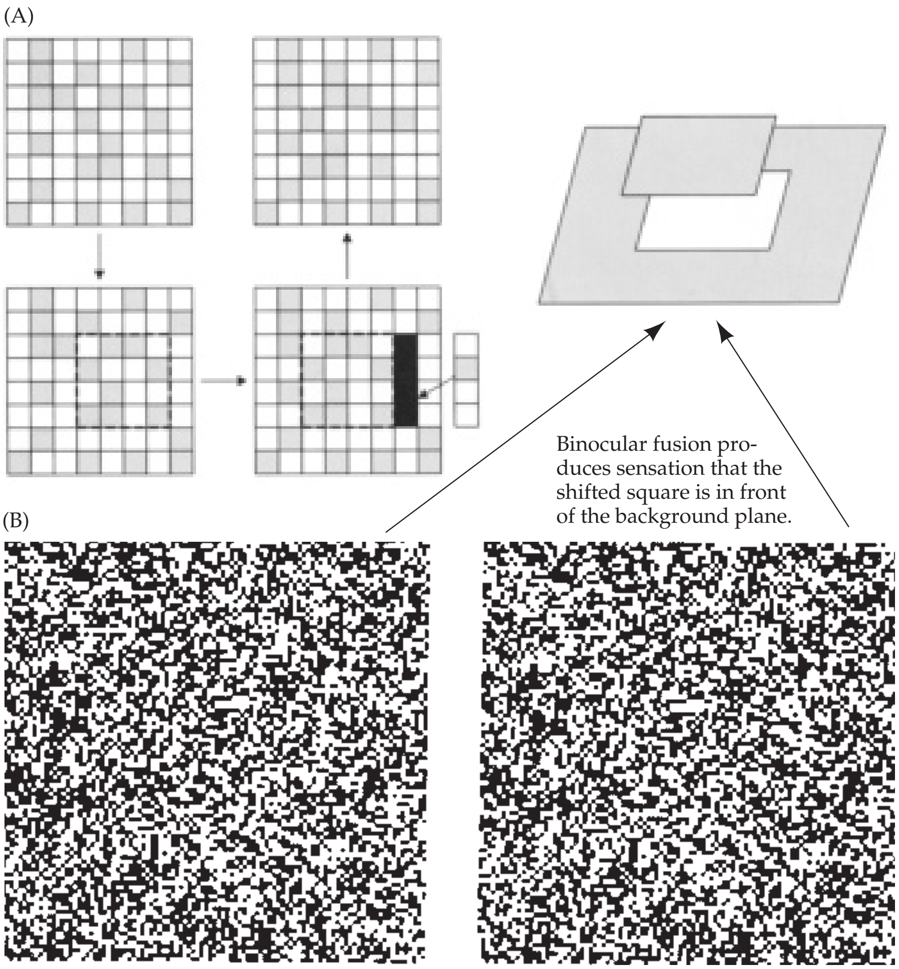
Figure 11.11 Binocular disparities are generally thought to be the basis of stereopsis. When the eyes are fixated on point b, points that lie beyond the plane of fixation (point c) or in front of the point of fixation (point a) project to noncorresponding points on the two retinas. When these disparities are small, the images are fused and the disparity is interpreted by the brain as small differences in depth. When the disparities are greater, double vision occurs (although this normal phenomenon is generally unnoticed).

Box B

Random Dot Stereograms and Related Amusements

An important advance in studies of stereopsis was made in 1959 when Bela Julesz, then working at the Bell Laboratories in Murray Hill, New Jersey, discovered an ingenious way of showing that stereoscopy depends on matching information seen by the two eyes without any prior recognition of what object(s) such matching might generate. Julesz, a Hungarian whose background was in engineering and physics, was working on the problem of how to "break" camouflage. He surmised that the brain's ability to fuse the slightly different views of the two eyes to bring out new information would be an aid in overcoming military camouflage. Julesz also realized that, if his hypothesis was correct, a hidden figure in a random pattern presented to the two eyes should emerge when a portion of the otherwise identical pattern was shifted horizontally in the view of one eye or the other. A horizontal shift in one direction would cause the hidden object to appear in front of the plane of the background, whereas a shift in the other direction would cause the hidden object to appear in back of the plane. Such a figure, called a random dot stereogram, and the method of its creation are shown in Figures A and B. The two images can be easily fused in a stereoscope (like the familiar Viewmaster® toy) but can also be fused simply by allowing the eyes to diverge. Most people find it easiest to do this by imagining that they are looking "through" the figure; after some seconds, during which the brain tries to make sense of what it is presented with, the two images merge and the hidden figure appears (in this case, a square that occupies the middle portion of the figure). The random dot stereogram has been widely used in stereoscopic research for about 40 years, although how such stimuli elicit depth remains very much a matter of dispute.

An impressive—and extraordinarily popular—derivative of the random dot stereogram is the autostereogram (Figure C). The possibility of autostereograms was first discerned by the nineteenth-century British physicist David Brewster. While staring at a Victorian wallpaper with an iterated but offset pattern, he noticed that when the patterns were fused, he perceived two different planes. The plethora of autostereograms that can be seen today in posters, books, and newspapers are close cousins of the random dot stereogram in that computers are used to shift patterns of iterated



Binocular fusion produces sensation that the shifted square is in front of the background plane.

Random dot stereograms and autostereograms. (A) to construct a random dot stereogram, a random dot pattern is created to be observed by one eye. The stimulus for the other eye is created by copying the first image, displacing a particular region horizontally, and then filling in the gap with a random sample of dots. (B) When the right and left images are viewed simultaneously but independently by the two eyes (by using a stereoscope or fusing the images by converging or diverging the eyes), the shifted region (a square) appears to be in a different plane from the other dots. (A after Wandell, 1995.)

information with respect to each other. The result is that different planes emerge from what appears to be a meaningless array of visual information (or, depending on the taste of the creator, an apparently "normal" scene in which the iterated and displaced information is hidden). Some autostereograms are designed to reveal the hidden figure when the eyes diverge, and others when they converge. (Looking at a plane more distant than the plane of the surface causes divergence; looking at a plane in front of the picture causes the eyes to converge; see Figure 11.11.)

The elevation of the autostereogram to a popular art form should probably be attributed to Chris W. Tyler, a student of Julesz's and a visual psychophysicist, who was among the first to create commercial autostereograms. Numerous graphic artists—preeminently in Japan, where the popularity of the autostereogram has been enormous—have generated many of such images. As with the random dot stereogram, the task in viewing the autostereogram is not clear to the observer. Nonetheless, the hidden figure emerges, often after minutes of effort in which the brain automatically tries to make sense of the occult information.

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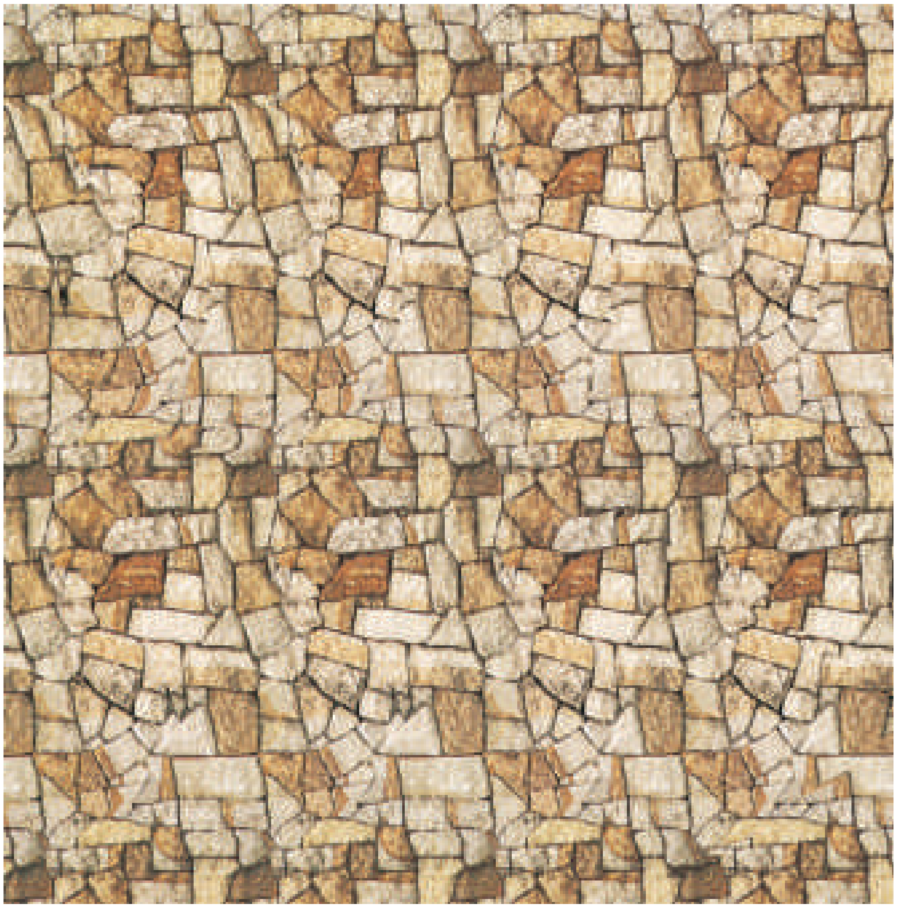

(C) An autostereogram. The hidden figure (three geometrical forms) emerges by diverging the eyes in this case. (C courtesy of Jun Oi.)

similar at any one point in primary visual cortex, but tend to shift smoothly across its surface. With respect to orientation, for example, all the neurons encountered in an electrode penetration perpendicular to the surface at a particular point will very likely have the same orientation preference, forming a "column" of cells with similar response properties. Adjacent columns, however, usually have slightly different orientation preferences; the sequence of orientation preferences encountered along a tangential electrode penetration gradually shifts as the electrode advances (Figure 11.12). Thus, orientation preference is mapped in the cortex, much like receptive field

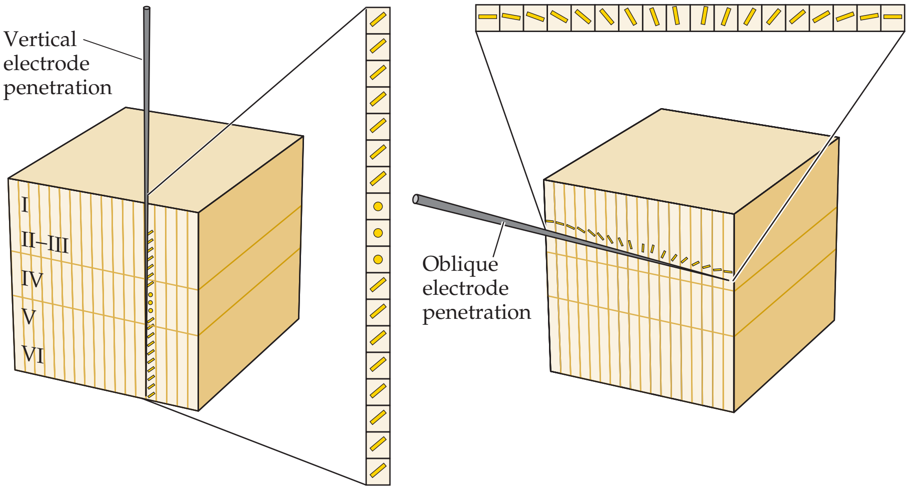

Figure 11.12 Columnar organization of orientation selectivity in the monkey striate cortex. Vertical electrode penetrations encounter neurons with the same preferred orientations, whereas oblique penetrations show a systematic change in orientation across the cortical surface. The circles denote the lack of orientation-selective cells in layer IV.

location (Box C). Unlike the map of visual space, however, the map of orientation preference is iterated many times, such that the same orientation preference is repeated at approximately 1-mm intervals across the striate cortex. This iteration presumably ensures that there are neurons for each region of visual space that represent the full range of orientation values. The orderly progression of orientation preference (as well as other properties that are mapped in this systematic way) is accommodated within the orderly map of visual space by the fact that the mapping is relatively coarse. Each small region of visual space is represented by a set of neurons whose receptive fields cover the full range of orientation preferences, the set being distributed over several millimeters of the cortical surface

The columnar organization of the striate cortex is equally apparent in the binocular responses of cortical neurons. Although most neurons in the striate cortex respond to stimulation of both eyes, the relative strength of the inputs from the two eyes varies from neuron to neuron. At the extremes of this continuum are neurons that respond almost exclusively to the left or right eye; in the middle are those that respond equally well to both eyes. As in the case of orientation preference, vertical electrode penetrations tend to encounter neurons with similar ocular preference (or **ocular dominance**, as it is usually called), whereas tangential penetrations show gradual shifts in ocular dominance. And, like the arrangement of orientation preference, a movement of about a millimeter across the surface is required to sample the full complement of ocular dominance values (Figure 11.13). These shifts in ocular dominance result from the ocular segregation of the inputs from lateral geniculate nucleus within cortical layer IV (see Figure 11.10).

Although the modular arrangement of the visual cortex was first recognized on the basis of these orientation and ocular dominance columns, further work has shown that other stimulus features such as color, direction of motion, and spatial frequency also tend to be distributed in iterated patterns that are systematically related to each other (for example, orientation columns tend to intersect ocular dominance columns at right angles). In short, the striate cortex is composed of repeating units, or modules, that contain all the neuronal machinery necessary to analyze a small region of visual space for a variety of different stimulus attributes. As described in Box D in Chapter 8, a number of other cortical regions show a similar columnar arrangement of their processing circuitry.

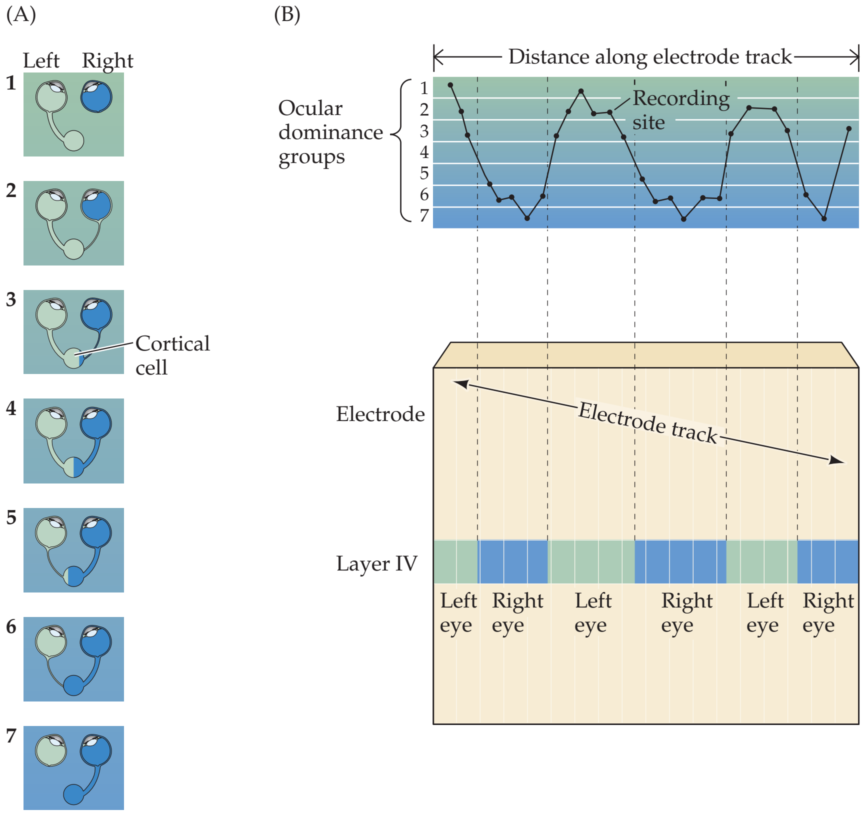

Figure 11.13 Columnar organization of ocular dominance. (A) Cortical neurons in all layers vary in the strength of their response to the inputs from the two eyes, from complete domination by one eye to equal influence of the two eyes. (B) Tangential electrode penetration across the superficial cortical layers reveals a gradual shift in the ocular dominance of the recorded neurons from one eye to the other. In contrast, all neurons encountered in a vertical electrode penetration (other than those neurons that lie in layer IV) tend to have the same ocular dominance.

Division of Labor within the Primary Visual Pathway

In addition to being specific for input from one eye or the other, the layers in the lateral geniculate are also distinguished on the basis of cell size: Two ventral layers are composed of large neurons and are referred to as the **magnocellular layers**, while more dorsal layers are composed of small neurons and are referred to as the **parvocellular layers**. The magno- and parvocellular layers receive inputs from distinct populations of ganglion cells that exhibit corresponding differences in cell size. M ganglion cells that terminate in the magnocellular layers have larger cell bodies, more extensive dendritic fields, and larger-diameter axons than the P ganglion cells that terminate in the parvocellular layers (Figure 11.14A). Moreover, the axons of relay cells in the magno- and parvocellular layers of the lateral geniculate nucleus terminate on distinct populations of neurons located in separate strata within layer 4 of striate cortex. Thus the retinogeniculate pathway is composed of parallel **magnocellular and parvocellular streams** that convey distinct types of information to the initial stages of cortical processing.

The response properties of the M and P ganglion cells provide important clues about the contributions of the magno- and parvocellular streams to visual perception. M ganglion cells have larger receptive fields than P cells, and their axons have faster conduction velocities. M and P ganglion cells also differ in ways that are not so obviously related to their morphology. M cells respond transiently to the presentation of visual stimuli, while P cells respond in a sustained fashion. Moreover, P ganglion cells can transmit information about color, whereas M cells cannot. P cells convey color information because their receptive field centers and surrounds are driven by different classes of cones (i.e., cones responding with greatest sensitivity to

Box C

Optical Imaging of Functional Domains in the Visual Cortex

The recent availability of optical imaging techniques has made it possible to visualize how response properties, such as the selectivity for edge orientation or ocular dominance, are mapped across the cortical surface. These methods generally rely on intrinsic signals (changes in the amount of light reflected from the cortical surface) that correlate with levels of neural activity. Such signals are thought to arise at least in part from local changes in the ratio of oxyhemoglobin and deoxyhemoglobin that accompany such activity, more active areas having a higher deoxyhemoglobin/oxyhemoglobin ratio (see also Box A in Chapter 1). This change can be detected when the cortical surface is illuminated with red light (605–700 nm). Under these conditions, active cortical regions absorb more light than less active ones. With the use of a sensitive video camera, and averaging over a number of trials (the changes are small, 1 or 2 parts per thousand), it is possible to visualize these differences and use them to map cortical patterns of activity (Figure A).

This approach has now been successfully applied to both striate and extrastriate areas in both experimental animals and human patients undergoing neurosurgery. The results emphasize that maps of stimulus features are a general principle of cortical organization. For example, orientation preference is mapped in a continuous fashion such that adjacent positions on the cortical surface tend to have only slightly shifted orientation preferences. However, there are points where continuity breaks down. Around these points, orientation preference is represented in a radial pattern resembling a pinwheel, covering the whole 180° of possible orientation values (Figure B).

This powerful technique can also be used to determine how maps for different stimulus properties are arranged relative to one another, and to detect additional maps such as that for direction of motion. A comparison of ocular dominance bands and orientation preference maps, for example, shows that pinwheel centers are generally located in the center of ocular dominance bands, and that the iso-orientation contours that emanate from the pinwheel centers run orthogonal to the borders of ocular dominance bands (Figure C). An orderly relationship between maps of orientation selectivity and direction selectivity has also been demonstrated. These systematic relationships between the functional maps that coexist within primary visual cortex are thought to ensure that all combinations of stimulus features (orientation, direction, ocular dominance, and spatial frequency) are analyzed for all regions of visual space.

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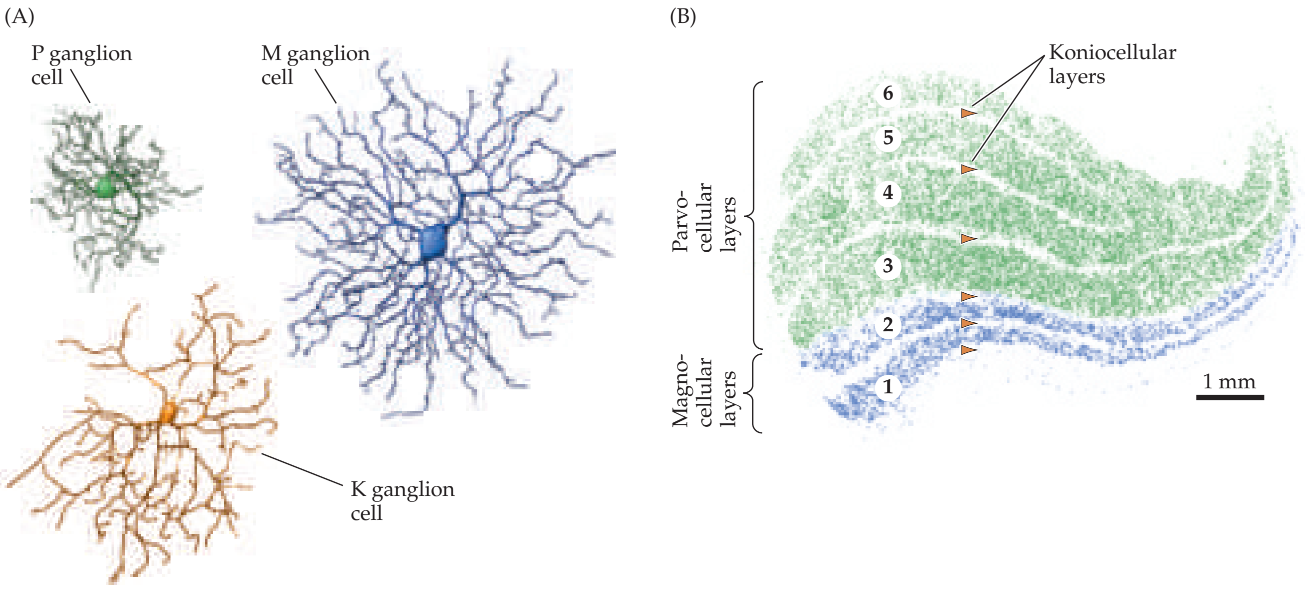

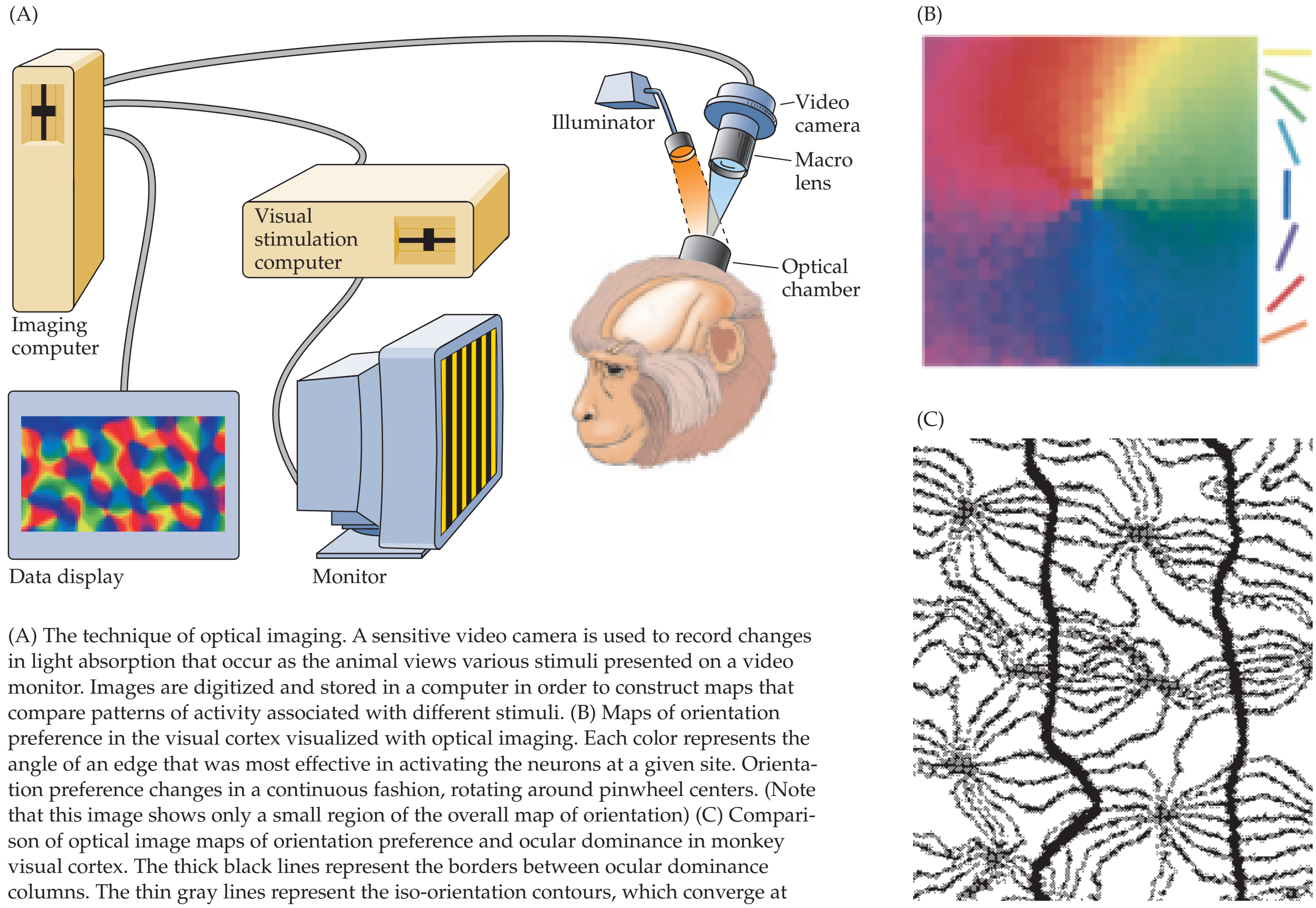

(A) The technique of optical imaging. A sensitive video camera is used to record changes in light absorption that occur as the animal views various stimuli presented on a video monitor. Images are digitized and stored in a computer in order to construct maps that compare patterns of activity associated with different stimuli. (B) Maps of orientation preference in the visual cortex visualized with optical imaging. Each color represents the angle of an edge that was most effective in activating the neurons at a given site. Orientation preference changes in a continuous fashion, rotating around pinwheel centers. (Note that this image shows only a small region of the overall map of orientation) (C) Comparison of optical image maps of orientation preference and ocular dominance in monkey visual cortex. The thick black lines represent the borders between ocular dominance columns. The thin gray lines represent the iso-orientation contours, which converge at orientation pinwheel centers (arrow). Iso-orientation contour lines generally intersect the borders of ocular dominance bands at right angles. (B from Bonhoeffer and Grinvald, 1993; C from Obermeyer and Blasdel, 1993.)

short-, medium-, or long-wavelength light). For example, some P ganglion cells have centers that receive inputs from long-wavelength ("red") sensitive cones and surrounds that receive inputs from medium-wavelength ("green") cones. Others have centers that receive inputs from "green cones" and surrounds from "red cones" (see Chapter 10). As a result, P cells are sensitive to differences in the wavelengths of light striking their receptive field center

◀ **Figure 11.14** Magno- and parvocellular streams. (A) Tracings of M and P ganglion cells as seen in flat mounts of the retina after staining by the Golgi method. M cells have large-diameter cell bodies and large dendritic fields. They supply the magnocellular layers of the lateral geniculate nucleus. P cells have smaller cell bodies and dendritic fields. They supply the parvocellular layers of the lateral geniculate nucleus. (B) Photomicrograph of the human lateral geniculate nucleus showing the magnocellular and parvocellular layers. (A after Watanabe and Rodieck, 1989; B courtesy of T. Andrews and D. Purves.)

and surround. Although M ganglion cells also receive inputs from cones, there is no difference in the type of cone input to the receptive field center and surround; the center and surround of each M cell receptive field is driven by all cone types. The absence of cone specificity to center-surround antagonism makes M cells largely insensitive to differences in the wavelengths of light that strike their receptive field centers and surrounds, and they are thus unable to transmit color information to their central targets.

The contribution of the magno- and parvocellular streams to visual perception has been tested experimentally by examining the visual capabilities of monkeys after selectively damaging either the magno- or parvocellular layers of the lateral geniculate nucleus. Damage to the magnocellular layers has little effect on visual acuity or color vision, but sharply reduces the ability to perceive rapidly changing stimuli. In contrast, damage to the parvocellular layers has no effect on motion perception but severely impairs visual acuity and color perception. These observations suggest that the visual information conveyed by the parvocellular stream is particularly important for high spatial resolution vision—the detailed analysis of the shape, size, and color of objects. The magnocellular stream, on the other hand, appears critical for tasks that require high temporal resolution, such as evaluating the location, speed and direction of a rapidly moving object.

In addition to the magno- and parvocellular streams, a third distinct anatomical pathway—the **koniocellular**, or **K-cell pathway**—has been identified within the lateral geniculate nucleus. Neurons contributing to the K-cell pathway reside in the interlaminar zones that separate lateral geniculate layers; these neurons receive inputs from fine-caliber retinal axons and project in a patchy fashion to the superficial layers (layers II and III) of striate cortex. Although the contribution of the K-cell pathway to perception is not understood, it appears that some aspects of color vision, especially information derived from short-wavelength-sensitive cones, may be transmitted via the K-cell rather than the P-cell pathway. Why short-wavelength-sensitive cone signals should be processed differently from middle- and long-wavelength information is not clear, but the distinction may reflect the earlier evolutionary origin of the K-cell pathway (see Chapter 10).

The Functional Organization of Extrastriate Visual Areas

Anatomical and electrophysiological studies in monkeys have led to the discovery of a multitude of areas in the occipital, parietal, and temporal lobes that are involved in processing visual information (Figure 11.15). Each of these areas contains a map of visual space, and each is largely dependent on the primary visual cortex for its activation. The response properties of the neurons in some of these regions suggest that they are specialized for different aspects of the visual scene. For example, the **middle temporal area** (**MT**) contains neurons that respond selectively to the direction of a moving edge without regard to its color. In contrast, neurons in another cortical area called **V4** respond selectively to the color of a visual stimulus without regard to its direction of movement. These physiological findings are supported by behavioral evidence; thus, damage to area MT leads to a specific impairment in a monkey's ability to perceive the direction of motion in a stimulus pattern, while other aspects of visual perception remain intact.

Recent functional imaging studies have indicated a similar arrangement of visual areas within human extrastriate cortex. Using retinotopically restricted stimuli, it has been possible to localize at least 10 separate repre-

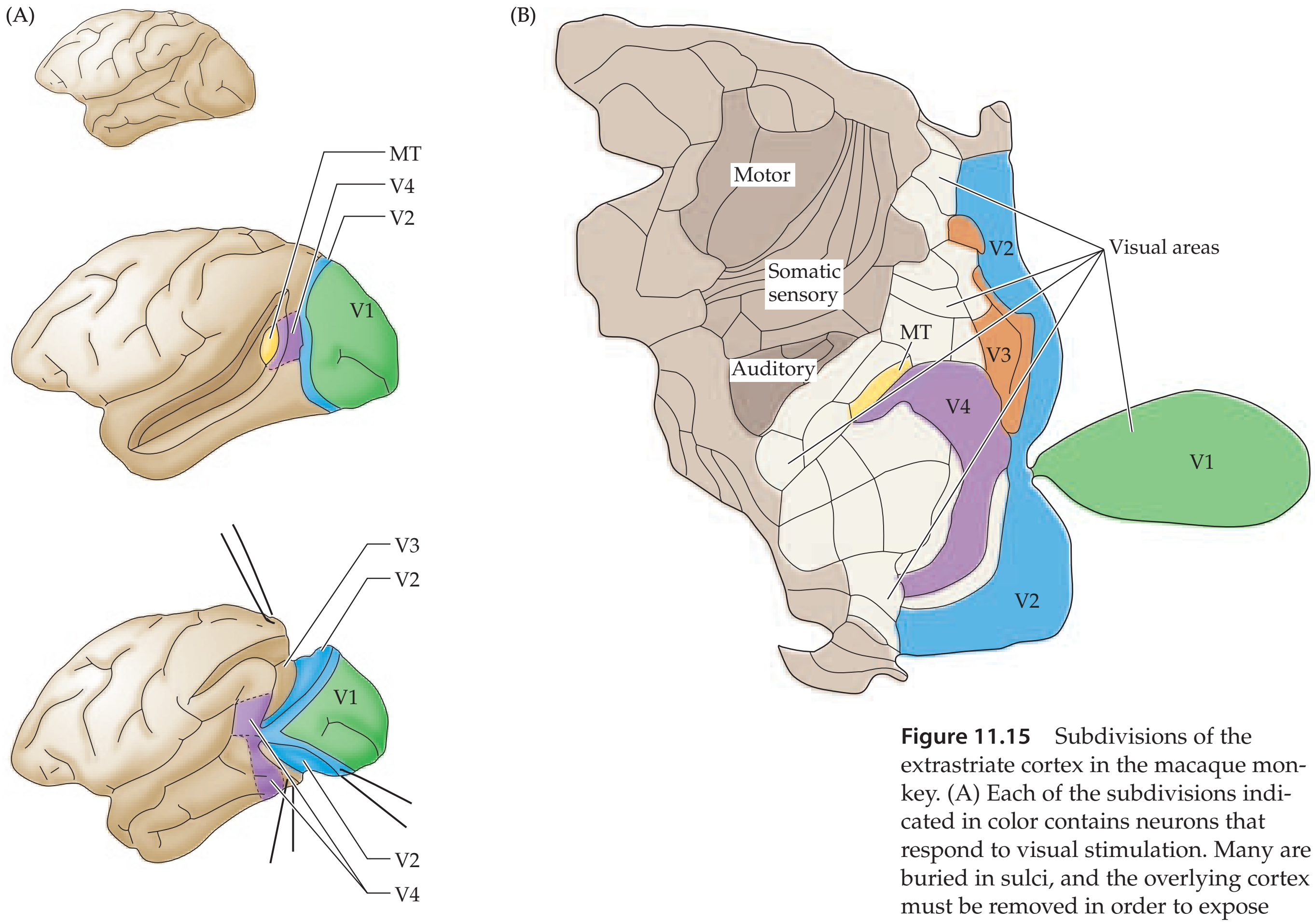

Figure 11.15 Subdivisions of the extrastriate cortex in the macaque monkey. (A) Each of the subdivisions indicated in color contains neurons that respond to visual stimulation. Many are buried in sulci, and the overlying cortex must be removed in order to expose them. Some of the more extensively studied extrastriate areas are specifically identified (V2, V3, V4, and MT). V1 is the primary visual cortex; MT is the middle temporal area. (B) The arrangement of extrastriate and other areas of neocortex in a flattened view of the monkey neocortex. There are at least 25 areas that are predominantly or exclusively visual in function, plus 7 other areas suspected to play a role in visual processing. (A after Maunsell and Newsome, 1987; B after Felleman and Van Essen, 1991.)

sentations of the visual field (Figure 11.16). One of these areas exhibits a large motion-selective signal, suggesting that it is the homologue of the motion-selective middle temporal area described in monkeys. Another area exhibits color-selective responses, suggesting that it may be similar to V4 in non-human primates. A role for these areas in the perception of motion and color, respectively, is further supported by evidence for increases in activity not only during the presentation of the relevant stimulus, but also during periods when subjects experience motion or color afterimages.

The clinical description of selective visual deficits after localized damage to various regions of extrastriate cortex also supports functional specialization of extrastriate visual areas in humans. For example, a well-studied patient who suffered a stroke that damaged the extrastriate region thought to be comparable to area MT in the monkey was unable to appreciate the motion of objects. The neurologist who treated her noted that she had difficulty in pouring tea into a cup because the fluid seemed to be “frozen.” In addition, she could not stop pouring at the right time because she was unable to perceive when the fluid level had risen to the brim. The patient also had trouble following a dialogue because she could not follow the movements of the speaker’s mouth. Crossing the street was potentially terrifying because she couldn’t judge the movement of approaching cars. As the patient related, “When I’m looking at the car first, it seems far away. But

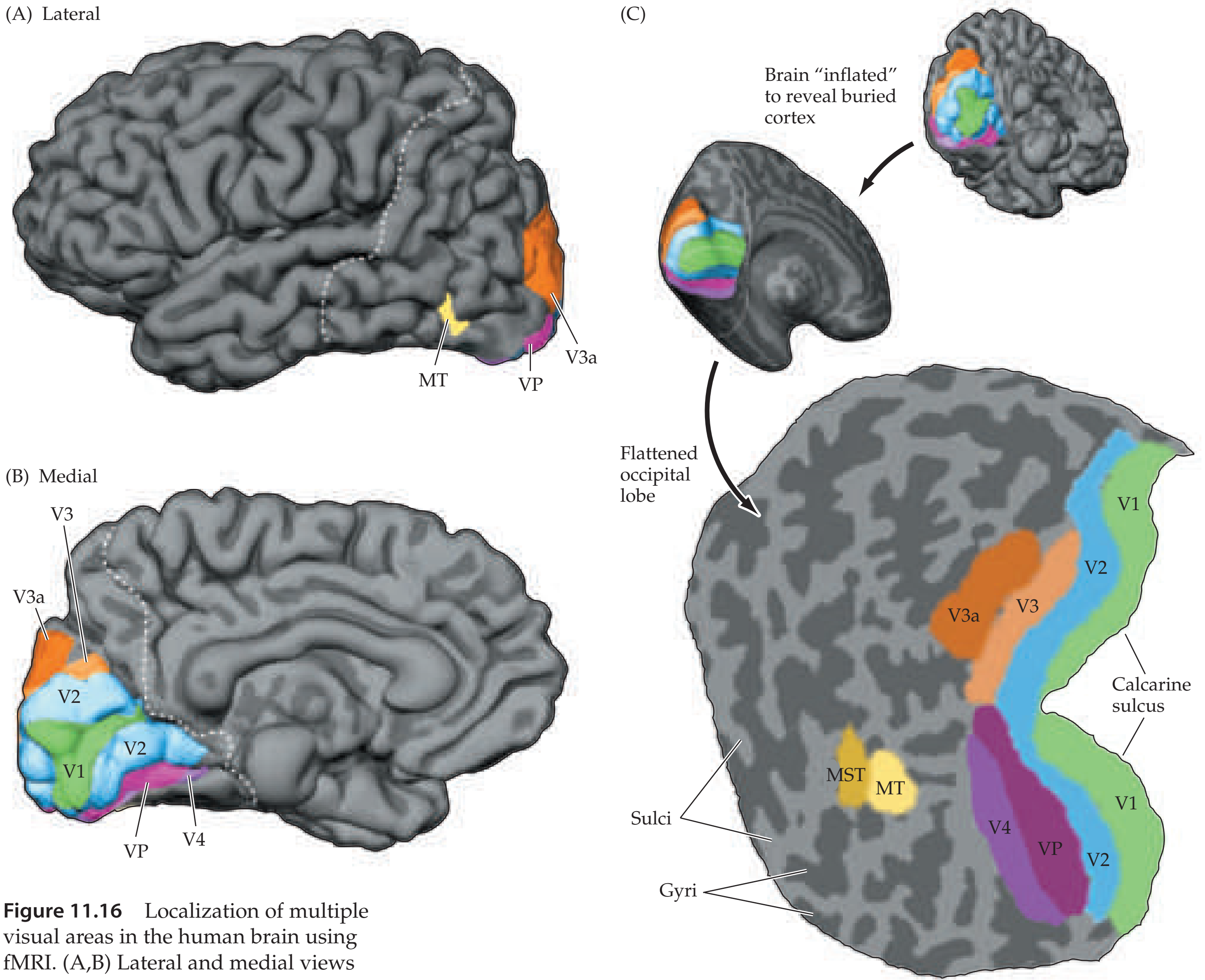

Figure 11.16 Localization of multiple visual areas in the human brain using fMRI. (A,B) Lateral and medial views (respectively) of the human brain, illustrating the location of primary visual cortex (V1) and additional visual areas V2, V3, VP (ventral posterior area), V4, MT (middle temporal area), and MST (medial superior temporal area). (C) Unfolded and flattened view of retinotopically defined visual areas in the occipital lobe. Dark grey areas correspond to cortical regions that were buried in sulci; light regions correspond to regions that were located on the surface of gyri. Visual areas in humans show a close resemblance to visual areas originally defined in monkeys (compare with Figure 11.15). (After Sereno et al., 1995.)

then, when I want to cross the road, suddenly the car is very near." Her ability to perceive other features of the visual scene, such as color and form, was intact.

Another example of a specific visual deficit as a result of damage to extrastriate cortex is **cerebral achromatopsia**. These patients lose the ability to see the world in color, although other aspects of vision remain in good working order. The normal colors of a visual scene are described as being replaced by "dirty" shades of gray, much like looking at a poor quality black-and-white movie. Achromatopsic individuals know the normal colors of objects—that a school bus is yellow, an apple red—but can no longer see them. Thus, when asked to draw objects from memory, they have no difficulty with shapes but are unable to appropriately color the objects they have represented. It is important to distinguish this condition from the color blindness that arises from the congenital absence of one or more cone pigments in the retina (see Chapter 10). In achromatopsia, the three types of cones are functioning normally; it is damage to specific extrastriate cortical areas that renders the patient unable to use the information supplied by the retina.

Based on the anatomical connections between visual areas, differences in electrophysiological response properties, and the effects of cortical lesions, a consensus has emerged that extrastriate cortical areas are organized into two largely separate systems that eventually feed information into cortical association areas in the temporal and parietal lobes (see Chapter 25). One system, called the ventral stream, includes area V4 and leads from the striate cortex into the inferior part of the temporal lobe. This system is thought to be responsible for high-resolution form vision and object recognition. The dorsal stream, which includes the middle temporal area, leads from striate cortex into the parietal lobe. This system is thought to be responsible for spatial aspects of vision, such as the analysis of motion, and positional relationships between objects in the visual scene (Figure 11.17).

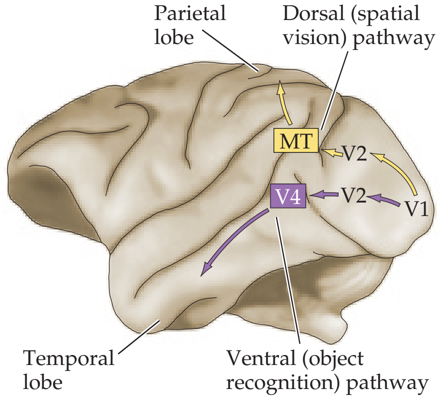
Parietal lobe
Dorsal (spatial vision) pathway
MT
V2
V4
V2
V1
Temporal lobe
Ventral (object recognition) pathway

Figure 11.17 The visual areas beyond the striate cortex are broadly organized into two pathways: a ventral pathway that leads to the temporal lobe, and a dorsal pathway that leads to the parietal lobe. The ventral pathway plays an important role in object recognition, the dorsal pathway in spatial vision.

The functional dichotomy between these two streams is supported by observations on the response properties of neurons and the effects of selective cortical lesions. Neurons in the ventral stream exhibit properties that are important for object recognition, such as selectivity for shape, color, and texture. At the highest levels in this pathway, neurons exhibit even greater selectivity, responding preferentially to faces and objects (see Chapter 25). In contrast, those in the dorsal stream are not tuned to these properties, but show selectivity for direction and speed of movement. Consistent with this interpretation, lesions of the parietal cortex severely impair an animal's ability to distinguish objects on the basis of their position, while having little effect on its ability to perform object recognition tasks. In contrast, lesions of the inferotemporal cortex produce profound impairments in the ability to perform recognition tasks but no impairment in spatial tasks. These effects are remarkably similar to the syndromes associated with damage to the parietal and temporal lobe in humans (see Chapters 25 and 26).

What, then, is the relationship between these "higher-order" extrastriate visual pathways and the magno- and parvocellular pathways that supply the primary visual cortex? Not long ago, it seemed that these intracortical pathways were simply a continuation of the geniculostriate pathways—that is, the magnocellular pathway provided input to the dorsal stream and the parvocellular pathway provided input to the ventral stream. However, more recent work has indicated that the situation is more complicated. The temporal pathway clearly has access to the information conveyed by both the magno- and parvocellular streams; and the parietal pathway, while dominated by inputs from the magnocellular stream, also receives inputs from the parvocellular stream. Thus, interaction and cooperation between the magno- and parvocellular streams appear to be the rule in complex visual perceptions.

Summary

Distinct populations of retinal ganglion cells send their axons to a number of central visual structures that serve different functions. The most important projections are to the pretectum for mediating the pupillary light reflex, to the hypothalamus for the regulation of circadian rhythms, to the superior colliculus for the regulation of eye and head movements, and—most important of all—to the lateral geniculate nucleus for mediating vision and visual perception. The retinogeniculostriate projection (the primary visual pathway) is arranged topographically such that central visual structures contain an organized map of the contralateral visual field. Damage anywhere along the primary visual pathway, which includes the optic nerve, optic tract, lateral geniculate nucleus, optic radiation, and striate cortex, results in a loss of vision confined to a predictable region of visual space. Compared to retinal ganglion cells, neurons at higher levels of the visual pathway become increasingly selective in their stimulus requirements. Thus, most neurons in the striate cortex respond to light–dark edges only if they are presented at a certain orientation; some are selective for the length of the edge, and others to movement of the edge in a specific direction. Indeed, a point in visual space is related to a set of cortical neurons, each of which is specialized for processing a limited set of the attributes in the visual stimulus. The neural circuitry in the striate cortex also brings together information from the two eyes; most cortical neurons (other than those in layer IV, which are segregated into eye-specific columns) have binocular responses. Binocular convergence is presumably essential for the detection of binocular disparity, an important component of depth perception. The primary visual pathway is composed of separate functional streams that convey information from different types of retinal ganglion cells to the initial stages of cortical processing. The magnocellular stream conveys information that is critical for the detection of rapidly changing stimuli, the parvocellular stream mediates high acuity vision and appears to share responsibility for color vision with the koniocellular stream. Finally, beyond striate cortex, parcellation of function continues in the ventral and dorsal streams that lead to the extrastriate and association areas in the temporal and parietal lobes, respectively. Areas in the inferotemporal cortex are especially important in object recognition, whereas areas in the parietal lobe are critical for understanding the spatial relations between objects in the visual field.

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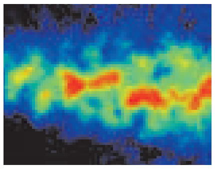
Chapter 12



The Auditory System

Overview

The auditory system is one of the engineering masterpieces of the human body. At the heart of the system is an array of miniature acoustical detectors packed into a space no larger than a pea. These detectors can faithfully transduce vibrations as small as the diameter of an atom, and they can respond a thousand times faster than visual photoreceptors. Such rapid auditory responses to acoustical cues facilitate the initial orientation of the head and body to novel stimuli, especially those that are not initially within the field of view. Although humans are highly visual creatures, much human communication is mediated by the auditory system; indeed, loss of hearing can be more socially debilitating than blindness. From a cultural perspective, the auditory system is essential not only to understanding speech, but also to music, one of the most aesthetically sophisticated forms of human expression. For these and other reasons, audition represents a fascinating and especially important mode of sensation.

Sound

In physical terms, *sound* refers to pressure waves generated by vibrating air molecules (somewhat confusingly, sound is used more casually to refer to an auditory percept). Sound waves are much like the ripples that radiate outward when a rock is thrown in a pool of water. However, instead of occurring across a two-dimensional surface, sound waves propagate in three dimensions, creating spherical shells of alternating compression and rarefaction. Like all wave phenomena, sound waves have four major features: **waveform**, **phase**, **amplitude** (usually expressed in log units known as decibels, abbreviated dB), and **frequency** (expressed in cycles per second or Hertz, abbreviated Hz). For human listeners, the amplitude and frequency of a sound pressure change at the ear roughly correspond to **loudness** and **pitch**, respectively.

The waveform of a sound stimulus is its amplitude plotted against time. It helps to begin by visualizing an acoustical waveform as a sine wave. At the same time, it must be kept in mind that sounds composed of single sine waves (i.e., pure tones) are extremely rare in nature; most sounds in speech, for example, consist of acoustically complex waveforms. Interestingly, such complex waveforms can often be modeled as the sum of sinusoidal waves of varying amplitudes, frequencies, and phases. In engineering applications, an algorithm called the Fourier transform decomposes a complex signal into its sinusoidal components. In the auditory system, as will be apparent later in the chapter, the inner ear acts as a sort of acoustical prism, decomposing complex sounds into a myriad of constituent tones.

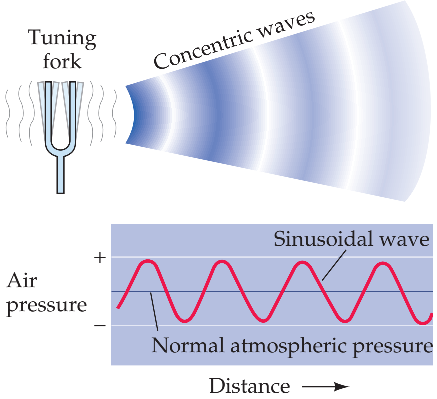


Figure 12.1 Diagram of the periodic condensation and rarefaction of air molecules produced by the vibrating tines of a tuning fork. The molecular disturbance of the air is pictured as if frozen at the instant the constituent molecules responded to the resultant pressure wave. Shown below is a plot of the air pressure versus distance from the fork. Note its sinusoidal quality.

Figure 12.1 diagrams the behavior of air molecules near a tuning fork that vibrates sinusoidally when struck. The vibrating tines of the tuning fork produce local displacements of the surrounding molecules, such that when the tine moves in one direction, there is molecular condensation; when it moves in the other direction, there is rarefaction. These changes in density of the air molecules are equivalent to local changes in air pressure.

Such regular, sinusoidal cycles of compression and rarefaction can be thought of as a form of circular motion, with one complete cycle equivalent to one full revolution (360°). This point can be illustrated with two sinusoids of the same frequency projected onto a circle, a strategy that also makes it easier to understand the concept of phase (Figure 12.2). Imagine that two tuning forks, both of which resonate at the same frequency, are struck at slightly different times. At a given time $t = 0$, one wave is at position P and the other at position Q. By projecting P and Q onto the circle, their respective phase angles, θ_1 and θ_2, are apparent. The sine wave that starts at P reaches a particular point on the circle, say 180°, at time t_1, whereas the wave that starts at Q reaches 180° at time t_2. Thus, phase differences have corresponding time differences, a concept that is important in appreciating how the auditory system locates sounds in space.

The human ear is extraordinarily sensitive to sound pressure. At the threshold of hearing, air molecules are displaced an average of only 10 picometers (10^{-11} m), and the intensity of such a sound is about one-trillionth of a watt per square meter! This means a listener on an otherwise noiseless planet could hear a 1-watt, 3-kHz sound source located over 450 km away (consider that even a very dim light bulb consumes more than 1 watt of power). Even dangerously high sound pressure levels (>100 dB) have power at the eardrum that is only in the milliwatt range (Box A).

The Audible Spectrum

Humans can detect sounds in a frequency range from about 20 Hz to 20 kHz. Human infants can actually hear frequencies slightly higher than 20 kHz, but lose some high-frequency sensitivity as they mature; the upper limit in average adults is closer to 15–17 kHz. Not all mammalian species are sensitive to the same range of frequencies. Most small mammals are sensitive to very high frequencies, but not to low frequencies. For instance, some species of bats are sensitive to tones as high as 200 kHz, but their lower limit is around 20 kHz—the upper limit for young people with normal hearing.

One reason for these differences is that small objects, including the auditory structures of these small mammals, resonate at high frequencies, whereas large objects tend to resonate at low frequencies—which explains why the violin has a higher pitch than the cello. Different animal species tend to emphasize frequency bandwidths in both their vocalizations and their range of hearing. In general, vocalizations by virtue of their periodicity can be distinguished from the noise "barrier" created by environmental sounds, such as wind and rustling leaves. Animals that echolocate, such as bats and dolphins, rely on very high-frequency vocal sounds to maximally resolve spatial features of the target, while animals intent on avoiding predation have auditory systems "tuned" to the low frequency vibrations that approaching predators transmit through the substrate. These behavioral differences are mirrored by a wealth of anatomical and functional specializations throughout the auditory system.

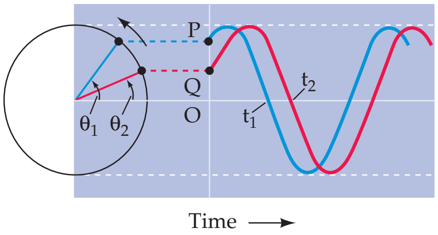


Figure 12.2 A sine wave and its projection as circular motion. The two sinusoids shown are at different phases, such that point P corresponds to phase angle θ_1 and point Q corresponds to phase angle θ_2.

Box A
Four Causes of Acquired Hearing Loss

Acquired hearing loss is an increasingly common sensory deficit that can often lead to impaired oral communication and social isolation. Four major causes of acquired hearing loss are acoustical trauma, infection of the inner ear, ototoxic drugs, and presbyacusis (literally, the hearing of the old).

The exquisite sensitivity of the auditory periphery, combined with the direct mechanical linkage between the acoustical stimulus and the receptor cells, make the ear especially susceptible to acute or chronic acoustical trauma. Extremely loud, percussive sounds, such as those generated by explosives or gunfire, can rupture the eardrum and so severely distort the inner ear that the organ of Corti is torn. The resultant loss of hearing is abrupt and often quite severe. Less well appreciated is the fact that repeated exposure to less dramatic but nonetheless loud sounds, including those produced by industrial or household machinery or by amplified musical instruments, can also damage the inner ear. Although these sounds leave the eardrum intact, specific damage is done to the hair bundle itself; the stereocilia of cochlear hair cells of animals exposed to loud sounds shear off at their pivot points with the hair cell body, or fuse together in a platelike fashion that impedes movement. In humans, the mechanical resonance of the ear to stimulus frequencies centered about 3 kHz means that exposure to loud, broadband noises (such as those generated by jet engines) results in especially pronounced deficits near this resonant frequency.

Ototoxic drugs include aminoglycoside antibiotics (such as gentamycin and kanamycin), which directly affect hair cells, and ethacrynic acid, which poisons the potassium-extruding cells of the stria vascularis that generate the endocochlear potential. In the absence of these ion pumping cells, the endocochlear potential, which supplies the energy to drive the transduction process, is lost. Although still a matter of some debate, the relatively nonselective transduction channel apparently affords a means of entry for aminoglycoside antibiotics, which then poison hair cells by disrupting phosphoinositide metabolism. In particular, outer hair cells and those inner hair cells that transduce high-frequency stimuli are more affected, simply because of their greater energy requirements.

Finally, *presbyacusis*, the hearing loss associated with aging, may in part stem from atherosclerotic damage to the especially fine microvasculature of the inner ear, as well as from genetic predispositions to hair cell damage. Recent advances in understanding the genetic transmission of acquired hearing loss in both humans and mice point to mutations in myosin isoforms unique to hair cells as a likely culprit.

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A Synopsis of Auditory Function

The auditory system transforms sound waves into distinct patterns of neural activity, which are then integrated with information from other sensory systems to guide behavior, including orienting movements to acoustical stimuli and intraspecies communication. The first stage of this transformation occurs at the external and middle ears, which collect sound waves and amplify their pressure, so that the sound energy in the air can be successfully transmitted to the fluid-filled cochlea of the inner ear. In the inner ear, a series of biomechanical processes occur that break up the signal into simpler, sinusoidal components, with the result that the frequency, amplitude, and phase of the original signal are all faithfully transduced by the sensory **hair cells** and encoded by the electrical activity of the **auditory nerve fibers**. One product of this process of acoustical decomposition is the systematic representation of sound frequency along the length of the cochlea, referred to as **tonotopy**, which is an important organizational feature preserved

Box B

Music

Even though we all recognize it when we hear it, the concept of music is vague. The *Oxford English Dictionary* defines it as "The art or science of combining vocal or instrumental sounds with a view toward beauty or coherence of form and expression of emotion." In terms of the present chapter, music chiefly concerns the aspect of human audition that is experienced as tones. The stimuli that give rise to tonal percepts are periodic, meaning that they repeat systematically over time, as in the sine wave in Figure 12.1. Periodic stimuli, which do not occur naturally as sine waves but rather as complex repetitions involving a number of different frequencies, give rise to a sense of harmony when sounded together in appropriate combinations, and a sense of melody when they occur sequentially.

Although we usually take the way tone-evoking stimuli are heard for granted, this aspect of audition presents some profoundly puzzling qualities. The most obvious of these is that humans perceive periodic stimuli whose fundamental frequencies have a 2:1 ratio as highly similar, and, for the most part, musically interchangeable. Thus in Western musical terminology, any two tones related by an interval of one or more octaves are given the same name (i.e., A, B, C…G), and are distinguished only by a qualifier that denotes relative ordinal position (e.g., C_1, C_2, C_3, etc.). As a result, music is framed in repeating intervals (called octaves) defined by these more or less interchangeable tones. A key question, then, is why periodic sound stimuli whose fundamentals have a 2:1 ratio are perceived as similar when there is no obvious physical or physiological basis for this phenomenon.

A second puzzling feature is that most if not all musical traditions subdivide octaves into a relatively small set of intervals for composition and performance, each interval being defined by its relationship to the lowest tone of the set. Such sets are called musical scales. The scales predominantly employed in all cultures over the centuries have used some (or occasionally all) of the 12 tonal intervals that in Western musical terminology are referred to as the chromatic scale (see figure). Moreover, some intervals of the chromatic scale, such as the fifth, the fourth, the major third, and the major sixth, are more often used in composition and performance than others. These form the majority of the intervals employed in the pentatonic and diatonic major scales, the two most frequently used scales in music world-wide. Again,

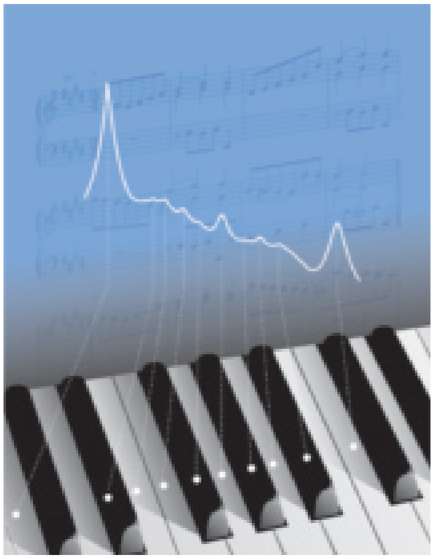

Illustration of 10 of the 12 tones in the chromatic scale, related to a piano keyboard. The function above the keyboard indicates that these tones correspond statistically to peaks of power in normalized human speech. (After Schwartz et al., 2003.)

throughout the central auditory pathways. The earliest stage of central processing occurs at the cochlear nucleus, where the peripheral auditory information diverges into a number of parallel central pathways. Accordingly, the output of the cochlear nucleus has several targets. One of these is the superior olivary complex, the first place that information from the two ears interacts and the site of the initial processing of the cues that allow listeners to localize sound in space. The cochlear nucleus also projects to the inferior colliculus of the midbrain, a major integrative center and the first place where auditory information can interact with the motor system. The inferior colliculus is an obligatory relay for information traveling to the thalamus and cortex, where additional integrative aspects (such as harmonic and temporal combinations) of sound especially germane to speech and music are processed (Box B). The large number of stations between the auditory periphery and the cortex far exceeds those in other sensory systems, providing a hint that the perception of communication and environmental sounds there is no principled explanation of these preferences among all the possible intervals within the octave.

Perhaps the most fundamental question in music—and arguably the common denominator of all musical tonality—is why certain combinations of tones are perceived as relatively consonant or 'harmonious' and others relatively dissonant or 'inharmonious'. These perceived differences among the possible combinations of tones making up the chromatic scale are the basis for polytonal music, in which the perception of relative harmoniousness guides the composition of chords and melodic lines. The more compatible of these combinations are typically used to convey 'resolution' at the end of a musical phrase or piece, whereas less compatible combinations are used to indicate a transition, a lack of resolution, or to introduce a sense of tension in a chord or melodic sequence. Like octaves and scales, the reason for this phenomenology remains a mystery.

The classical approaches to rationalizing octaves, scales and consonance have been based on the fact that the musical intervals corresponding to octaves, fifths, and fourths (in modern musical terminology) are produced by physical sources whose relative proportions (e.g., the relative lengths of two plucked strings or their fundamental frequencies) have ratios of 2:1, 3:2, or 4:3, respectively (these relationships were first described by Pythagoras). This coincidence of numerical simplicity and perceptual effect has been so impressive over the centuries that attempts to rationalize phenomena such as consonance and scale structure in terms of mathematical relationships have tended to dominate the thinking about these issues. This conceptual framework, however, fails to account for many of the perceptual observations that have been made over the last century.

Another way to consider the problem is in terms of the biological rationale for evolving a sense of tonality in the first place. A pertinent fact in this regard is that only a small minority of naturally occurring sound stimuli are periodic. Since the auditory system evolved in the world of natural sounds, this point is presumably critical for thinking about the biological purposes of tonality and music. Indeed, the majority of periodic sounds that humans would have been exposed to during evolution are those made by the human vocal tract in the process of communication, initially prelinguistic but more recently speech sounds (see Chapter 26). Thus developing a sense of tonality would enable listeners to respond not only the distinctions among the different speech sounds that are important for understanding spoken language, but to information about the probable sex, age, and emotional state of the speaker. It may thus be that music reflects the advantage of facilitating a listener's ability to glean the linguistic intent and biological state of fellow humans through vocal utterances.

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is an especially intensive neural process. Furthermore, both the peripheral and central auditory system are "tuned" to conspecific communication vocalizations, pointing to the interdependent evolution of neural systems used for generating and perceiving these signals.

The External Ear

The external ear, which consists of the **pinna**, **concha**, and **auditory meatus**, gathers sound energy and focuses it on the eardrum, or **tympanic membrane** (Figure 12.3). One consequence of the configuration of the human auditory meatus is that it selectively boosts the sound pressure 30- to 100-fold for frequencies around 3 kHz via passive resonance effects. This amplification makes humans especially sensitive to frequencies in the range of 2–5 kHz—and also explains why they are particularly prone to hearing loss near this frequency following exposure to loud broadband noises, such as those

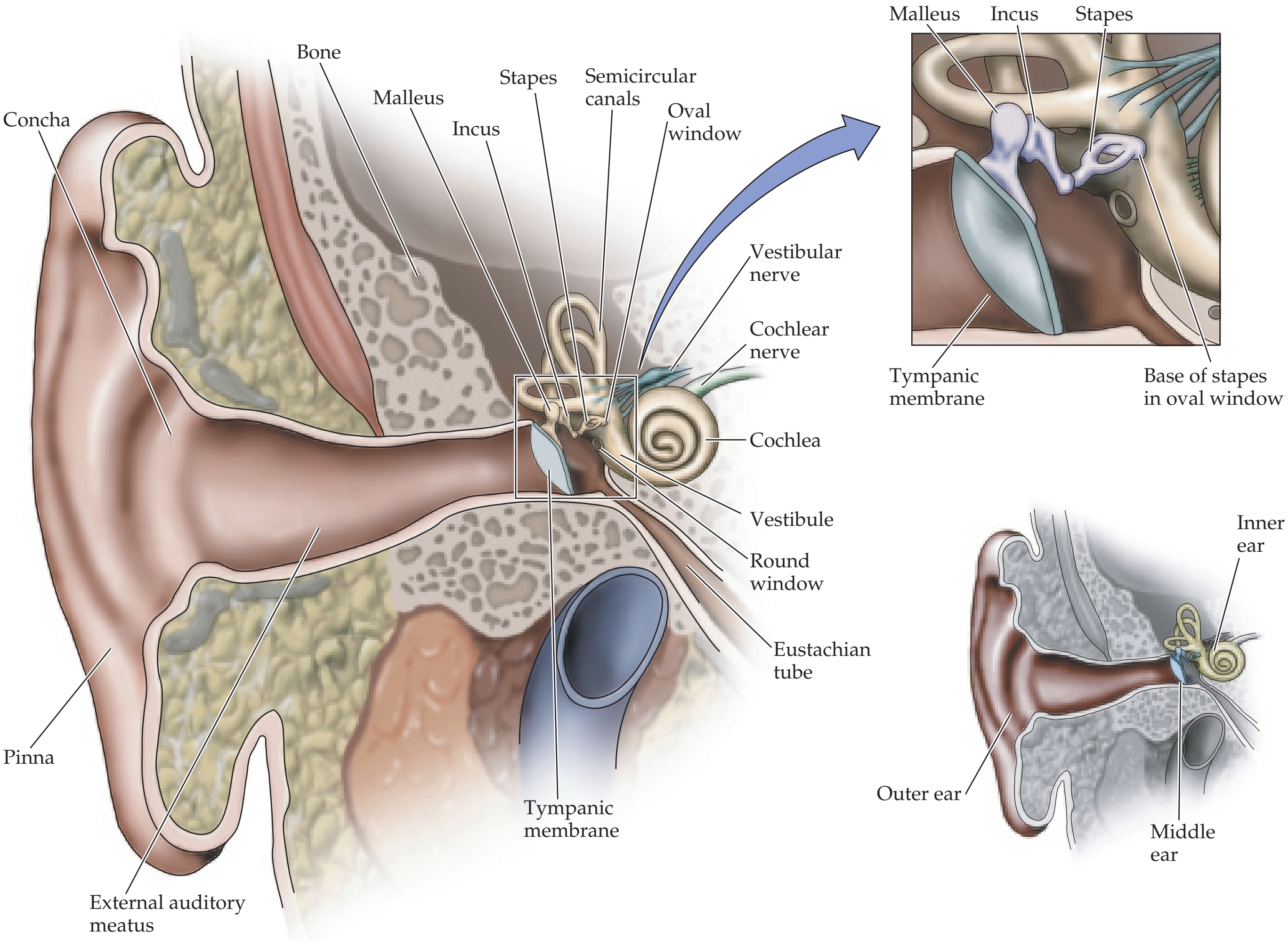

Malleus
Incus
Stapes
Concha
Bone
Malleus
Incus
Stapes
Semicircular canals
Oval window
Vestibular nerve
Cochlear nerve
Cochlea
Vestibule
Round window
Eustachian tube
Tympanic membrane
Base of stapes in oval window
Inner ear
Outer ear
Middle ear
Pinna
Tympanic membrane
External auditory meatus

Figure 12.3 The human ear. Note the large surface area of the tympanic membrane (eardrum) relative to the oval window, a feature that facilitates transmission of airborne sounds to the fluid-filled cochlea.

generated by heavy machinery or high explosives (see Box A). The sensitivity to this frequency range in the human auditory system appears to be directly related to speech perception: although human speech is a broadband signal, the energy of the plosive consonants (e.g., *ba* and *pa*) that distinguish different phonemes (the elementary human speech sounds) is concentrated around 3 kHz (see Box A in Chapter 26). Therefore, selective hearing loss in the 2–5 kHz range disproportionately degrades speech recognition. Most vocal communication occurs in the low-kHz range to overcome environmental noise; as already noted, generation of higher frequencies is difficult for animals the size of humans.

A second important function of the pinna and concha is to selectively filter different sound frequencies in order to provide cues about the elevation of the sound source. The vertically asymmetrical convolutions of the pinna are shaped so that the external ear transmits more high-frequency components from an elevated source than from the same source at ear level. This effect can be demonstrated by recording sounds from different elevations after they have passed through an “artificial” external ear; when the recorded sounds are played back via earphones, so that the whole series is at the same elevation relative to the listener, the recordings from higher elevations are perceived as coming from positions higher in space than the recordings from lower elevations.

The Middle Ear

Sounds impinging on the external ear are airborne; however, the environment within the inner ear, where the sound-induced vibrations are converted to neural impulses, is aqueous. The major function of the middle ear is to match relatively low-impedance airborne sounds to the higher-impedance fluid of the inner ear. The term "impedance" in this context describes a medium's resistance to movement. Normally, when sound waves travel from a low-impedance medium like air to a much higher-impedance medium like water, almost all (more than 99.9%) of the acoustical energy is reflected. The middle ear (see Figure 12.3) overcomes this problem and ensures transmission of the sound energy across the air–fluid boundary by boosting the pressure measured at the tympanic membrane almost 200-fold by the time it reaches the inner ear.

Two mechanical processes occur within the middle ear to achieve this large pressure gain. The first and major boost is achieved by focusing the force impinging on the relatively large-diameter tympanic membrane on to the much smaller-diameter **oval window**, the site where the bones of the middle ear contact the inner ear. A second and related process relies on the mechanical advantage gained by the lever action of the three small interconnected middle ear bones, or **ossicles** (i.e., the malleus, incus, and stapes; see Figure 12.3), which connect the tympanic membrane to the oval window. **Conductive hearing losses**, which involve damage to the external or middle ear, lower the efficiency at which sound energy is transferred to the inner ear and can be partially overcome by artificially boosting sound pressure levels with an external hearing aid (Box C). In normal hearing, the efficiency of sound transmission to the inner ear also is regulated by two small muscles in the middle ear, the tensor tympani, innervated by cranial nerve V, and the stapedius, innervated by cranial nerve VII (see Appendix A). Flexion of these muscles, which is triggered automatically by loud noises or during self-generated vocalization, stiffens the ossicles and reduces the amount of sound energy transmitted to the cochlea, serving to protect the inner ear. Conversely, conditions that lead to flaccid paralysis of either of these muscles, such as Bell's palsy (nerve VII), can trigger a painful sensitivity to moderate or even low intensity sounds known as **hyperacusis**.

Bony and soft tissues, including those surrounding the inner ear, have impedances close to that of water. Therefore, even without an intact tympanic membrane or middle ear ossicles, acoustical vibrations can still be transferred directly through the bones and tissues of the head to the inner ear. In the clinic, bone conduction can be exploited using a simple test involving a tuning fork to determine whether hearing loss is due to conductive problems or is due to damage to the hair cells of the inner ear or to the auditory nerve itself (**sensorineural hearing loss**; see Boxes A and C)

The Inner Ear

The **cochlea** of the inner ear is arguably the most critical structure in the auditory pathway, for it is there that the energy from sonically generated pressure waves is transformed into neural impulses. The cochlea not only amplifies sound waves and converts them into neural signals, but it also acts as a mechanical frequency analyzer, decomposing complex acoustical waveforms into simpler elements. Many features of auditory perception derive from aspects of the physical properties of the cochlea; hence, it is important to consider this structure in some detail.

Box C

Sensorineural Hearing Loss and Cochlear Implants

The same features that make the auditory periphery exquisitely sensitive to detecting airborne sounds also make it highly vulnerable to damage. By far the most common forms of hearing loss involve the peripheral auditory system, namely to those structures that transmit and transduce sounds into neural impulses. Monaural hearing deficits are the defining symptom of a peripheral hearing loss, because unilateral damage at or above the auditory brainstem results in a binaural deficit (due to the extensive bilateral organization of the central auditory system). Peripheral hearing insults can be further divided into conductive hearing losses, which involve damage to the outer or middle ear, and sensorineural hearing losses, which stem from damage to the inner ear, most typically the cochlear hair cells or the VIIIth nerve itself. Although both forms of peripheral hearing loss manifest themselves as a raised threshold for hearing on the affected side, their diagnoses and treatments differ.

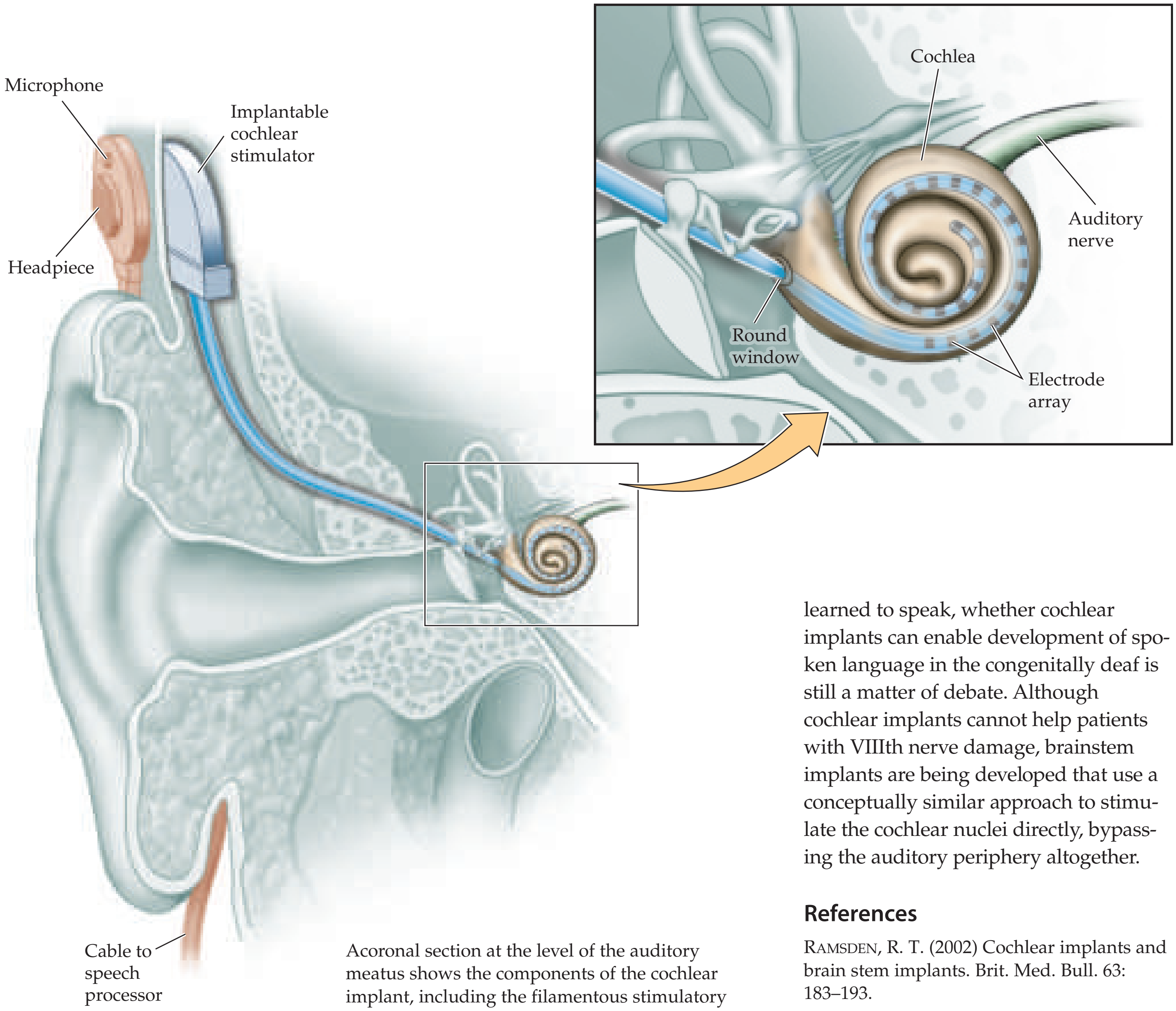
Conductive hearing loss can be due to occlusion of the ear canal by wax or foreign objects, rupture of the tympanic membrane itself, or arthritic ossification of the middle ear bones. In contrast, sensorineural hearing loss usually is due to congenital or environmental insults that lead to hair cell death (see Box A) or damage to the eighth nerve. As hair cells are relatively few in number and do not regenerate in humans, their depletion leads to a diminished ability to detect sounds. The Weber test, a simple test involving a tuning fork, can be used to distinguish between these two forms of hearing loss. If a resonating tuning fork (~256 Hz) is placed on the vertex, a patient with conductive hearing loss will report that the sound is louder in the affected ear. In the "plugged" state, sounds propagating through the skull do not dissipate so freely back out through the auditory meatus, and thus a greater amount of sound energy is transmitted to the cochlea on the blocked side. In contrast, a patient with a monaural sensorineural hearing loss will report that a Weber test sounds louder on the intact side, because even though the inner ear may vibrate equally on the two sides, the damaged side cannot transduce this vibration into a neural signal.

Treatment also differs for these two types of deafness. An external hearing aid is used to boost sounds to compensate for the reduced efficiency of the conductive apparatus in conductive hearing losses. These miniature devices are inserted in the ear canal, and contain a microphone and speaker, as well as an amplifier. One limitation of hearing aids is that they often provide rather flat amplification curves, which can interfere with listening in noisy environments; moreover, they do not achieve a high degree of directionality. The use of digital signal processing strategies partly overcomes these problems, and hearing aids obviously provide significant benefits to many people.

The treatment of sensorineural hearing loss is more complicated and invasive; conventional hearing aids are useless, because no amount of mechanical amplification can compensate for the inability to generate or convey a neural impulse from the cochlea. However, if the VIIIth nerve is intact, cochlear implants can be used to partially restore hearing. The cochlear implant consists of a peripherally mounted microphone and digital signal processor that transforms a sound into its spectral components, and additional electronics that use this information to activate different combinations of contacts on a threadlike multi-site stimulating electrode array. The electrode is inserted into the cochlea through the round window (see figure) and positioned along the length of the tonotopically organized basilar membrane and VIIIth nerve endings. This placement enables electrical stimulation of the nerve in a manner that mimics some aspects of the spectral decomposition naturally performed by the cochlea.

Cochlear implants can be remarkably effective in restoring hearing to people with hair cell damage, permitting them to engage in spoken communication. Despite such success in treating those who have lost their hearing *after* having

The cochlea (from the Latin for "snail") is a small (about 10 mm wide) coiled structure, which, were it uncoiled, would form a tube about 35 mm long (Figures 12.4 and 12.5). Both the oval window and, the **round window,** another region where the bone is absent surrounding the cochlea, are at the basal end of this tube. The cochlea is bisected from its basal almost to its apical end by the cochlear partition, which is a flexible structure that supports the **basilar membrane** and the **tectorial membrane**. There are fluid-filled chambers on each side of the cochlear partition, named the **scala vestibuli** and the **scala tympani**; a distinct channel, the **scala media**, runs within the



Acoronal section at the level of the auditory meatus shows the components of the cochlear implant, including the filamentous stimulatory electrode inserted into the cochlea through the round window.

learned to speak, whether cochlear implants can enable development of spoken language in the congenitally deaf is still a matter of debate. Although cochlear implants cannot help patients with VIIIth nerve damage, brainstem implants are being developed that use a conceptually similar approach to stimulate the cochlear nuclei directly, bypassing the auditory periphery altogether.

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cochlear partition. The cochlear partition does not extend all the way to the apical end of the cochlea; instead there is an opening, known as the **helicotrema**, that joins the scala vestibuli to the scala tympani, allowing their fluid, known as **perilymph**, to mix. One consequence of this structural arrangement is that inward movement of the oval window displaces the fluid of the inner ear, causing the round window to bulge out slightly and deforming the cochlear partition.

The manner in which the basilar membrane vibrates in response to sound is the key to understanding cochlear function. Measurements of the vibra-

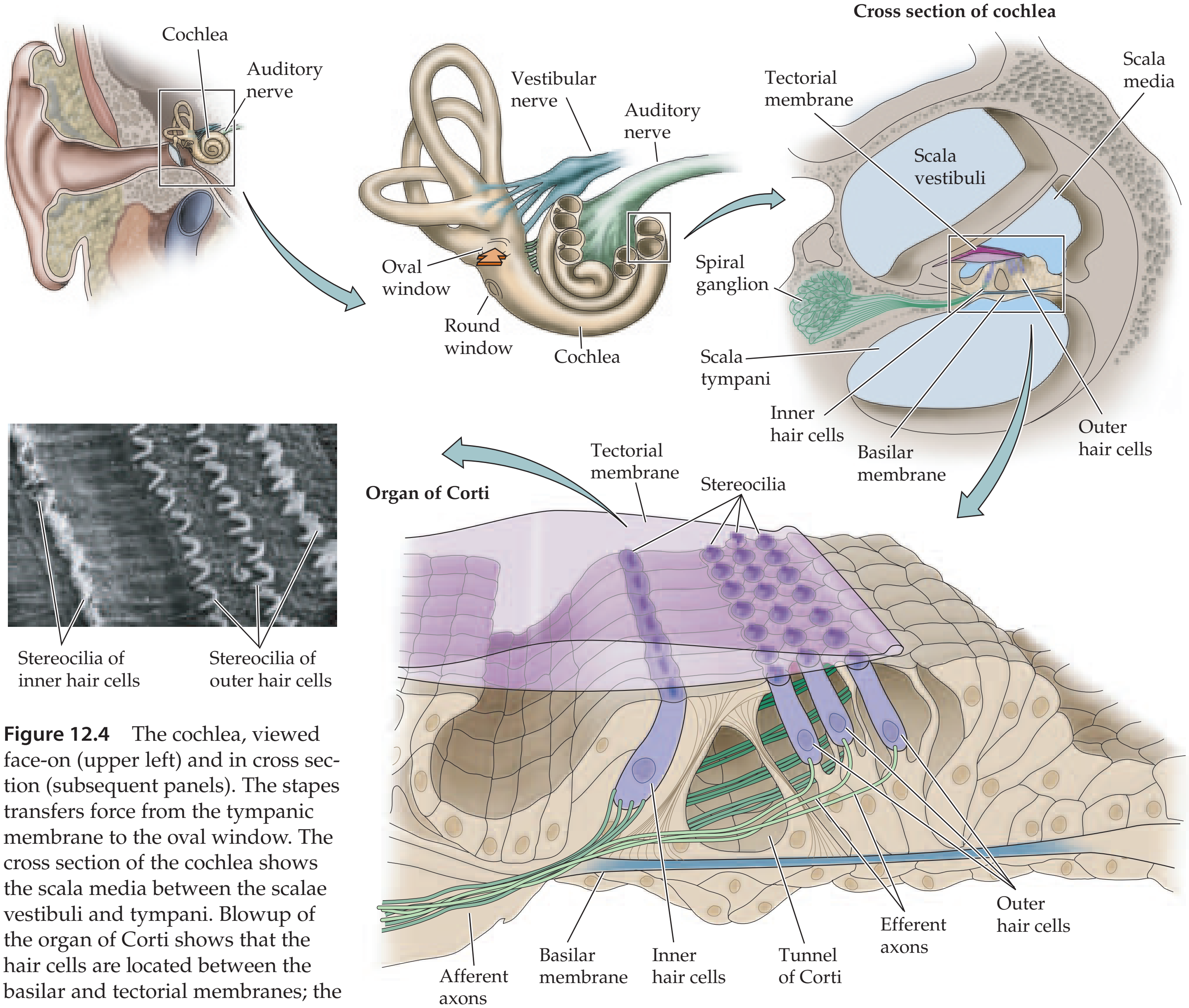
Cochlea
Auditory nerve
Vestibular nerve
Auditory nerve
Oval window
Round window
Cochlea
Spiral ganglion
Cross section of cochlea
Tectorial membrane
Scala media
Scala vestibuli
Scala tympani
Inner hair cells
Basilar membrane
Outer hair cells
Stereocilia of inner hair cells
Stereocilia of outer hair cells
Organ of Corti
Tectorial membrane
Stereocilia
Afferent axons
Basilar membrane
Inner hair cells
Tunnel of Corti
Efferent axons
Outer hair cells

Figure 12.4 The cochlea, viewed face-on (upper left) and in cross section (subsequent panels). The stapes transfers force from the tympanic membrane to the oval window. The cross section of the cochlea shows the scala media between the scalae vestibuli and tympani. Blowup of the organ of Corti shows that the hair cells are located between the basilar and tectorial membranes; the latter is rendered transparent in the line drawing and removed in the scanning electron micrograph. The hair cells are named for their tufts of stereocilia; inner hair cells receive afferent inputs from cranial nerve VIII, whereas outer hair cells receive mostly efferent input. (Micrograph from Kessel and Kardon, 1979.)

tion of different parts of the basilar membrane, as well as the discharge rates of individual auditory nerve fibers that terminate along its length, show that both these features are highly tuned; that is, they respond most intensely to a sound of a specific frequency. Frequency tuning within the inner ear is attributable in part to the geometry of the basilar membrane, which is wider and more flexible at the apical end and narrower and stiffer at the basal end. One feature of such a system is that regardless of where energy is supplied to it, movement always begins at the stiff end (i.e., the base), and then propagates to the more flexible end (i.e., the apex). Georg von Békésy, working at Harvard University, showed that a membrane that varies systematically in its width and flexibility vibrates maximally at different positions as a function of the stimulus frequency (Figure 12.5). Using tubular models and human cochleas taken from cadavers, he found that an acoustical stimulus initiates a **traveling wave** of the same frequency in the cochlea, which propagates from the base toward the apex of the basilar membrane, growing in

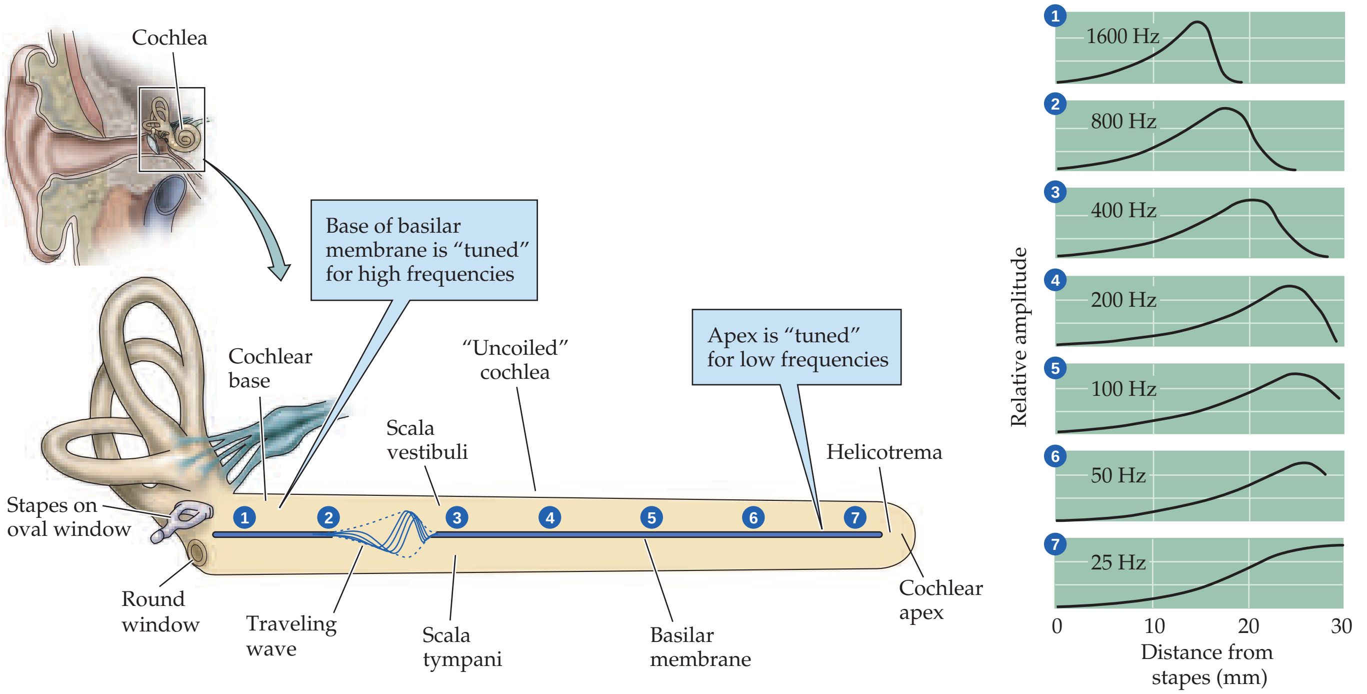
Cochlea
Base of basilar membrane is "tuned" for high frequencies
Cochlear base
"Uncoiled" cochlea
Apex is "tuned" for low frequencies
Scala vestibuli
Helicotrema
Stapes on oval window
1
2
3
4
5
6
7
Round window
Traveling wave
Scala tympani
Basilar membrane
Cochlear apex
1600 Hz
800 Hz
400 Hz
200 Hz
100 Hz
50 Hz
25 Hz
Relative amplitude
0
10
20
30
Distance from stapes (mm)

Figure 12.5 Traveling waves along the cochlea. A traveling wave is shown at a given instant along the cochlea, which has been uncoiled for clarity. The graphs on the right profile the amplitude of the traveling wave along the basilar membrane for different frequencies and show that the position (i.e., 1–7) where the traveling wave reaches its maximum amplitude varies directly with the frequency of stimulation. (Drawing after Dallos, 1992; graphs after von Békésy, 1960.)

amplitude and slowing in velocity until a point of maximum displacement is reached. This point of maximal displacement is determined by the sound frequency. The points responding to high frequencies are at the base of the basilar membrane where it is stiffer, and the points responding to low frequencies are at the apex, giving rise to a topographical mapping of frequency (that is, to **tonotopy**). An important feature is that complex sounds cause a pattern of vibration equivalent to the superposition of the vibrations generated by the individual tones making up that complex sound, thus accounting for the decompositional aspects of cochlear function mentioned earlier. This process of spectral decomposition appears to be an important strategy for detecting the various harmonic combinations that distinguish different natural sounds. Indeed, tonotopy is conserved throughout much of the auditory system, including the auditory cortex, suggesting that it is important to speech processing.

Von Békésy's model of cochlear mechanics was a passive one, resting on the premise that the basilar membrane acts like a series of linked resonators, much as a concatenated set of tuning forks. Each point on the basilar membrane was postulated to have a characteristic frequency at which it vibrated most efficiently; because it was physically linked to adjacent areas of the membrane, each point also vibrated (if somewhat less readily) at other frequencies, thus permitting propagation of the traveling wave. It is now clear, however, that the tuning of the auditory periphery, whether measured at the basilar membrane or recorded as the electrical activity of auditory nerve fibers, is too sharp to be explained by passive mechanics alone. At very low sound intensities, the basilar membrane vibrates one hundred-fold more than would be predicted by linear extrapolation from the motion measured at high intensities. Therefore, the ear's sensitivity arises from an active biomechanical process, as well as from its passive resonant properties (Box D). The outer hair cells, which together with the inner hair cells comprise the

Box D

The Sweet Sound of Distortion

As early as the first half of the eighteenth century, musical composers such as G. Tartini and W. A. Sorge discovered that upon playing pairs of tones, other tones not present in the original stimulus are also heard. These combination tones, fc, are mathematically related to the played tones f_1 and f_2 ($f_2 > f_1$) by the formula

$$fc = mf_1 \pm nf_2$$

where m and n are positive integers. Combination tones have been used for a variety of compositional effects, as they can strengthen the harmonic texture of a chord. Furthermore, organ builders sometimes use the difference tone ($f_2 - f_1$) created by two smaller organ pipes to produce the extremely low tones that would otherwise require building one especially large pipe.

Modern experiments suggest that this distortion product is due at least in part to the nonlinear properties of the inner ear. M. Ruggero and his colleagues placed small glass beads (10–30 mm in diameter) on the basilar membrane of an anesthetized animal and then determined the velocity of the basilar membrane in response to different combinations of tones by measuring the Doppler shift of laser light reflected from the beads. When two tones were played into the ear, the basilar membrane vibrated not only at those two frequencies, but also at other frequencies predicted by the above formula.

Related experiments on hair cells studied in vitro suggest that these nonlinearities result from the properties of the mechanical linkage of the transduction apparatus. By moving the hair bundle sinusoidally with a metal-coated glass fiber, A. J. Hudspeth and his coworkers found that the hair bundle exerts a force at the same frequency. However, when two sinusoids were applied simultaneously, the forces exerted by the hair bundle occurred not only at the primary frequencies, but at several combination frequencies as well. These distortion products are due to the transduction apparatus, since blocking the transduction channels causes the forces exerted at the combination frequencies to disappear, even though the forces at the primary frequencies remain unaffected. It seems that the tip links add a certain extra springiness to the hair bundle in the small range of motions over which the transduction channels are changing between closed and open states. If nonlinear distortions of basilar membrane vibrations arise from the properties of the hair bundle, then it is likely that hair cells can indeed influence basilar membrane motion, thereby accounting for the cochlea's extreme sensitivity. When we hear difference tones, we may be paying the price in distortion for an exquisitely fast and sensitive transduction mechanism.

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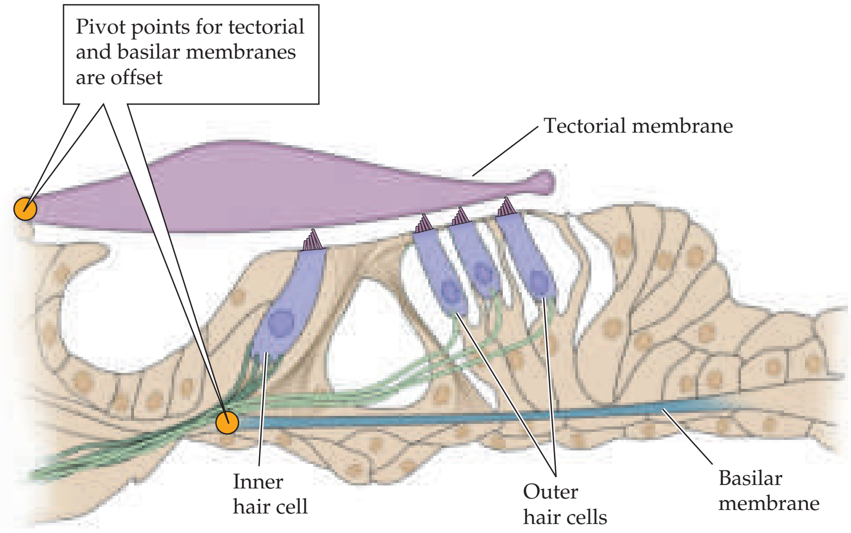
sensory cells of the inner ear, are the most likely candidates for driving this active process.

The motion of the traveling wave initiates sensory transduction by displacing the hair cells that sit atop the basilar membrane. Because these structures are anchored at different positions, the vertical component of the traveling wave is translated into a shearing motion between the basilar membrane and the overlying tectorial membrane (Figure 12.6). This motion bends the tiny processes, called **stereocilia**, that protrude from the apical ends of the hair cells, leading to voltage changes across the hair cell membrane. How the bending of stereocilia leads to receptor potentials in hair cells is considered in the following section.

Hair Cells and the Mechanoelectrical Transduction of Sound Waves

The hair cell is an evolutionary triumph that solves the problem of transforming vibrational energy into an electrical signal. The scale at which the

(A) Resting position


Pivot points for tectorial and basilar membranes are offset
Tectorial membrane
Inner hair cell
Outer hair cells
Basilar membrane

(B) Sound-induced vibration

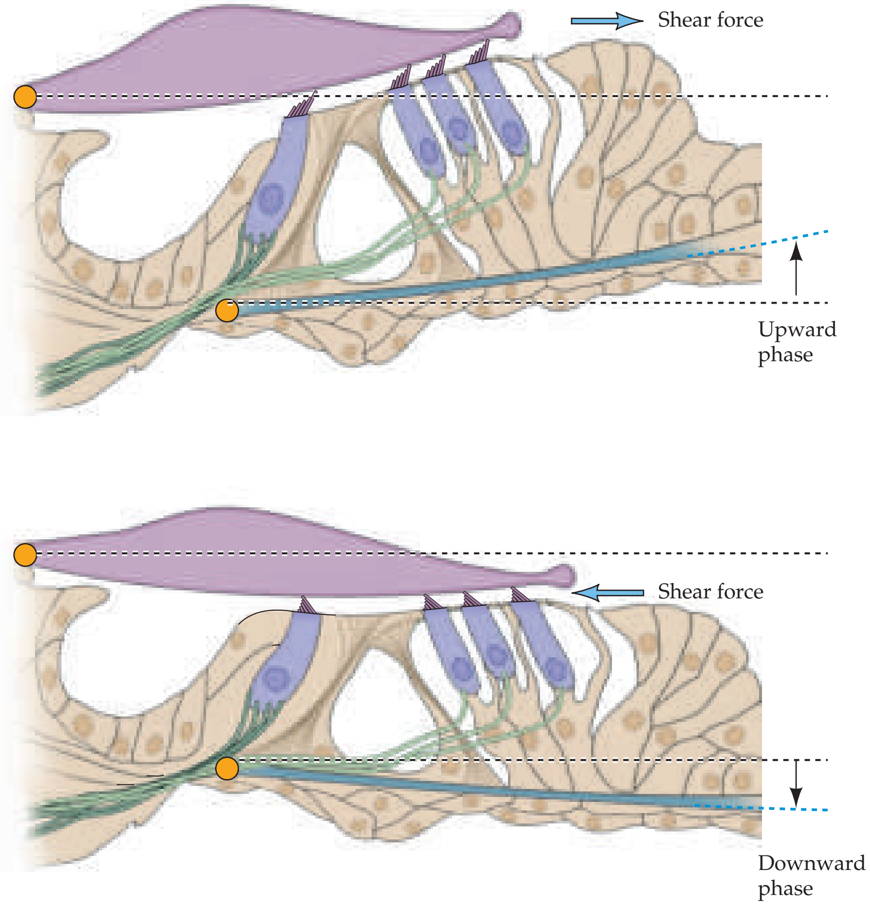

Shear force
Upward phase
Shear force
Downward phase

Figure 12.6 Movement of the basilar membrane creates a shearing force that bends the stereocilia of the hair cells. The pivot point of the basilar membrane is offset from the pivot point of the tectorial membrane, so that when the basilar membrane is displaced, the tectorial membrane moves across the tops of the hair cells, bending the stereocilia.

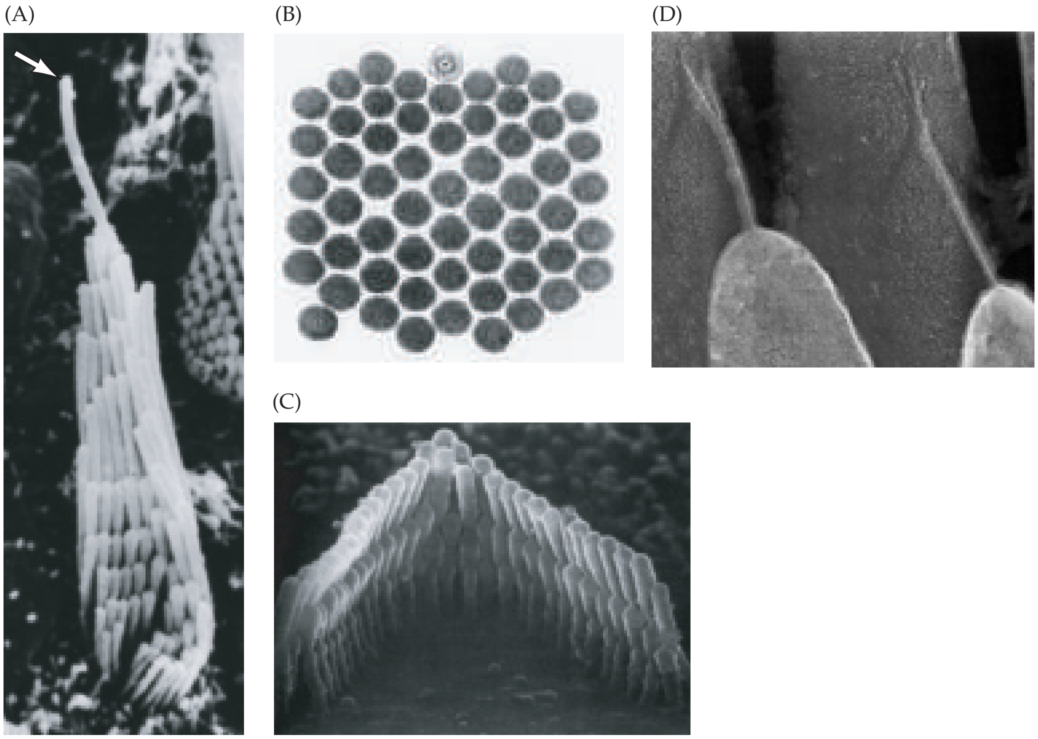


Figure 12.7 The structure and function of the hair bundle in vestibular and cochlear hair cells. The vestibular hair bundles shown here resemble those of cochlear hair cells, except for the presence of the kinocilium, which disappears in the mammalian cochlea shortly after birth. (A) The hair bundle of a guinea pig vestibular hair cell. This view shows the increasing height leading to the kinocilium (arrow). (B) Cross section through the vestibular hair bundle shows the 9 + 2 array of microtubules in the kinocilium (top), which contrasts with the simpler actin filament structure of the stereocilia. (C) Scanning electron micrograph of a guinea pig cochlear outer hair cell bundle viewed along the plane of mirror symmetry. Note the graded lengths of the stereocilia, and the absence of a kinocilium. (D) Tip links that connect adjacent stereocilia are believed to be the mechanical linkage that opens and closes the transduction channel. (A from Lindeman, 1973; B from Hudspeth, 1983; C from Pickles, 1988; D from Fain, 2003.)

hair cell operates is truly amazing: At the limits of human hearing, hair cells can faithfully detect movements of atomic dimensions and respond in the tens of microseconds! Furthermore, hair cells can adapt rapidly to constant stimuli, thus allowing the listener to extract signals from a noisy background.

The hair cell is a flask-shaped epithelial cell named for the bundle of hairlike processes that protrude from its apical end into the scala media. Each hair bundle contains anywhere from 30 to a few hundred hexagonally arranged stereocilia, with one taller **kinocilium** (Figure 12.7A). Despite their names, only the kinocilium is a true ciliary structure, with the characteristic two central tubules surrounded by nine doublet tubules that define cilia (Figure 12.7B). The function of the kinocilium is unclear, and in the cochlea of humans and other mammals it actually disappears shortly after birth (Figure 12.7C). The stereocilia are simpler, containing only an actin cytoskeleton. Each stereocilium tapers where it inserts into the apical membrane, forming a hinge about which each stereocilium pivots (Figure 12.7D). The stereocilia are graded in height and are arranged in a bilaterally symmetric fashion (in vestibular hair cells, this plane runs through the kinocilium). Displacement of the hair bundle parallel to this plane toward the tallest stereocilia depolarizes the hair cell, while movements parallel to this plane toward the shortest stereocilia cause hyperpolarization. In contrast, displacements perpendicular to the plane of symmetry do not alter the hair cell's membrane potential. The hair bundle movements at the threshold of hearing are approximately 0.3 nm, about the diameter of an atom of gold. Hair cells can convert the displacement of the stereociliary bundle into an electrical potential in as little as 10 microseconds; as described below, such speed is required for the accurate localization of the source of the sound. The need for microsecond resolution places certain constraints on the transduction mechanism, ruling out the relatively slow second messenger pathways used in visual and olfactory transduction (see Chapters 7, 10, and 14); a direct, mechanically gated transduction channel is needed to operate this quickly. Evidently the filamentous structures that connect the tips of adjacent stereocilia, known as **tip links**, directly open cation-selective transduction channels when stretched, allowing K^+ ions to flow into the cell (see Figure 12.7D). As the linked stereocilia pivot from side to side, the tension on the tip link varies, modulating the ionic flow and resulting in a graded receptor potential that follows the movements of the stereocilia (Figures 12.8 and 12.9). The tip link model also explains why only deflections along the axis of the hair bundle activate transduction channels, since tip links join adjacent stereocilia along the axis directed toward the tallest stereocilia (see also Box B in Chapter 13). The exquisite mechanical sensitivity of the stereocilia also presents substantial risks: high intensity sounds can shear off the hair bundle, resulting in profound hearing deficits. Because human stereocilia, unlike those in fishes and birds, do not regenerate such damage is irreversible. The small number of hair cells (a total of about 30,000 in a human, or 15,000 per ear) further compounds the sensitivity of the inner

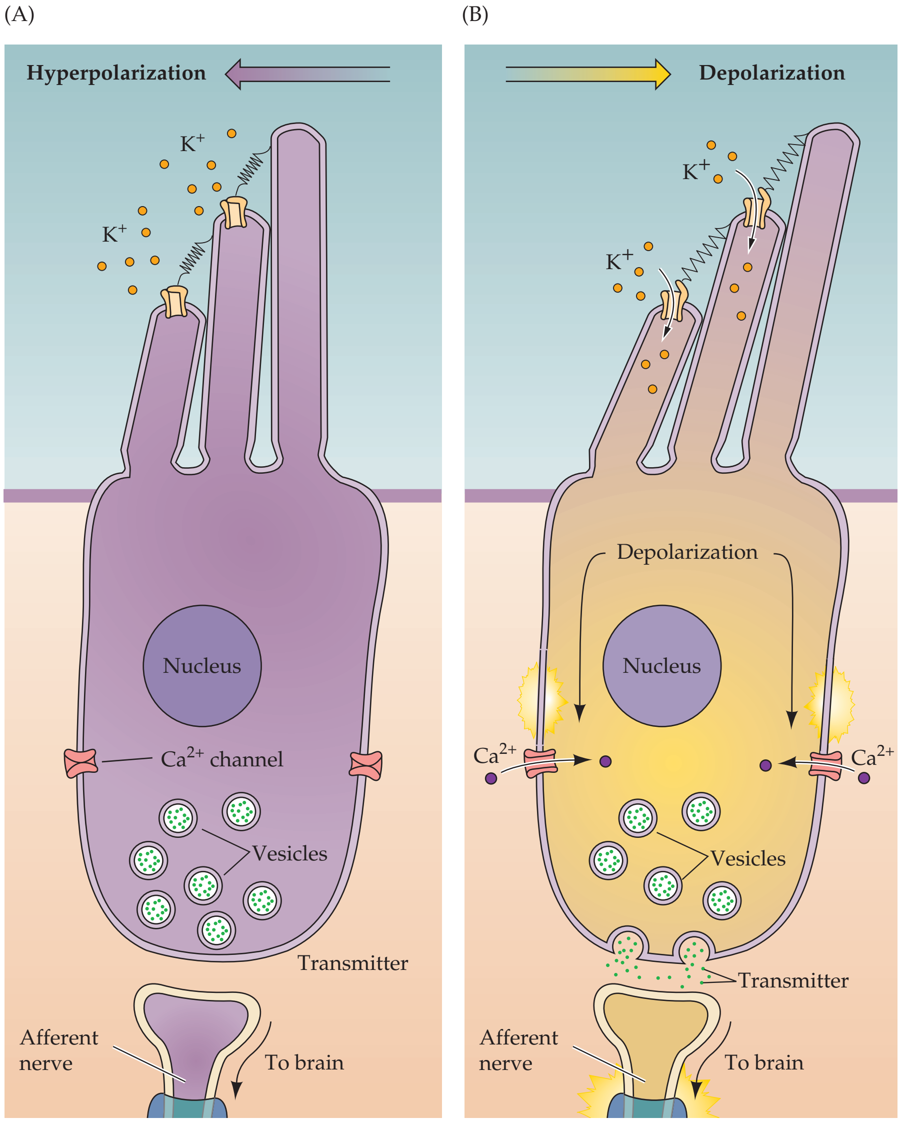


Figure 12.8 Mechanoelectrical transduction mediated by hair cells. (A,B) When the hair bundle is deflected toward the tallest stereocilium, cation-selective channels open near the tips of the stereocilia, allowing K^+ ions to flow into the hair cell down their electrochemical gradient (see text on next page for the explanation of this peculiar situation). The resulting depolarization of the hair cell opens voltage-gated Ca^{2+} channels in the cell soma, allowing calcium entry and release of neurotransmitter onto the nerve endings of the auditory nerve. (After Lewis and Hudspeth, 1983)

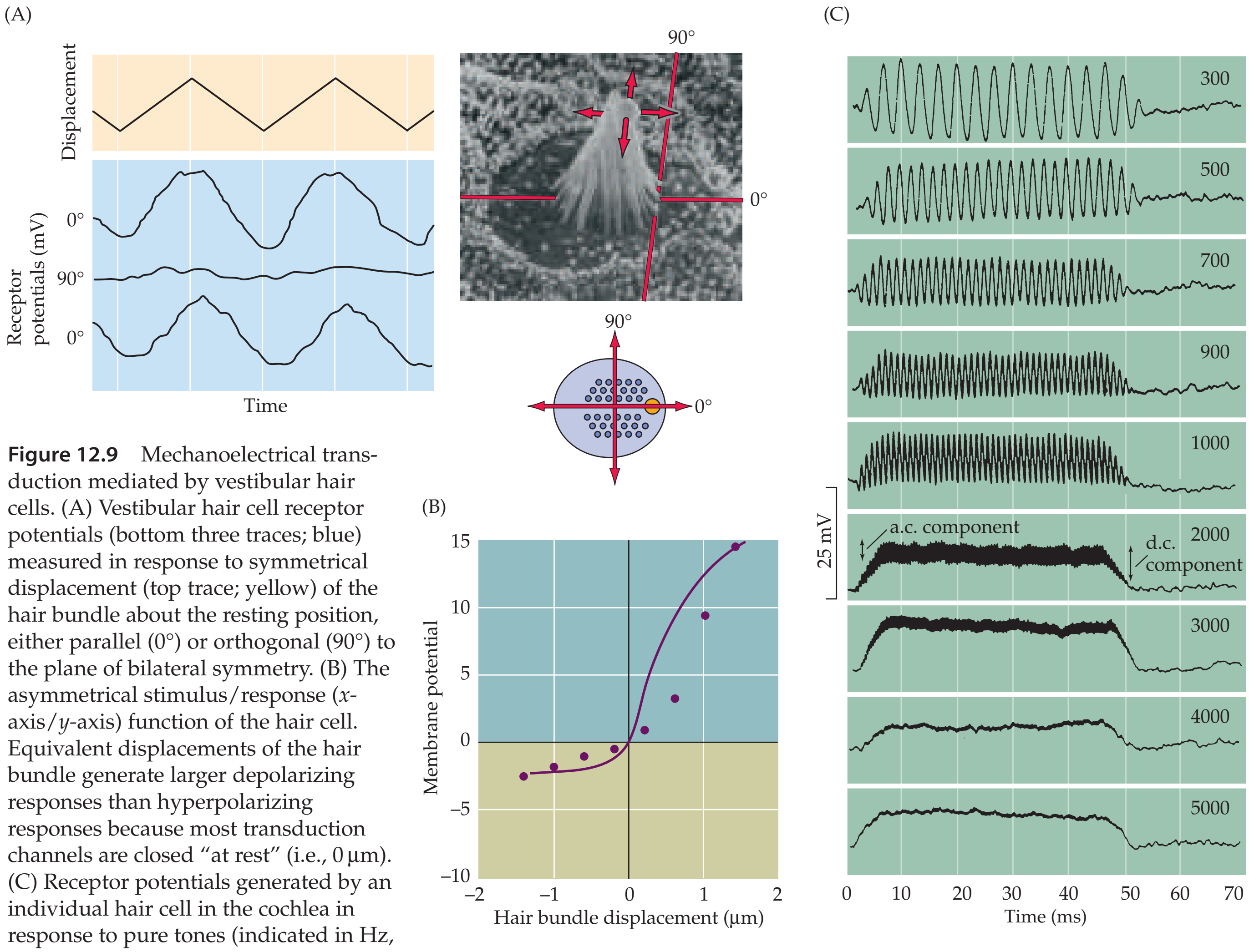


Figure 12.9 Mechanoelectrical transduction mediated by vestibular hair cells. (A) Vestibular hair cell receptor potentials (bottom three traces; blue) measured in response to symmetrical displacement (top trace; yellow) of the hair bundle about the resting position, either parallel (0°) or orthogonal (90°) to the plane of bilateral symmetry. (B) The asymmetrical stimulus/response (*x*-axis/*y*-axis) function of the hair cell. Equivalent displacements of the hair bundle generate larger depolarizing responses than hyperpolarizing responses because most transduction channels are closed "at rest" (i.e., 0 µm). (C) Receptor potentials generated by an individual hair cell in the cochlea in response to pure tones (indicated in Hz, right). Note that the hair cell potential faithfully follows the waveform of the stimulating sinusoids for low frequencies (< 3kHz), but still responds with a DC offset to higher frequencies. (A after Shotwell et al., 1981; B after Hudspeth and Corey, 1977; C after Palmer and Russell, 1986.)

ear to environmental and genetic insults. An important goal of current research is to identify the stem cells and factors that could contribute to the regeneration of human hair cells, thus affording a possible therapy for some forms of sensorineural hearing loss.

Understanding the ionic basis of hair cell transduction has been greatly advanced by intracellular recordings made from these tiny structures. The hair cell has a resting potential between –45 and –60 mV relative to the fluid that bathes the basal end of the cell. At the resting potential, only a small fraction of the transduction channels are open. When the hair bundle is displaced in the direction of the tallest stereocilium, more transduction channels open, causing depolarization as K^+ enters the cell. Depolarization in turn opens voltage-gated calcium channels in the hair cell membrane, and the resultant Ca^{2+} influx causes transmitter release from the basal end of the cell onto the auditory nerve endings (Figure 12.8A,B). Such calcium-dependent exocytosis is similar to chemical neurotransmission elsewhere in the central and peripheral nervous system (see Chapters 5 and 6); thus the hair cell has become a useful model for studying calcium-dependent transmitter release. Because some transduction channels are open at rest, the receptor potential is biphasic: Movement toward the tallest stereocilia depolarizes the cell, while movement in the opposite direction leads to hyperpolarization. This situation allows the hair cell to generate a sinusoidal receptor potential in response to a sinusoidal stimulus, thus preserving the temporal information present in the original signal up to frequencies of around 3 kHz (Figure 12.9). Hair cells still can signal at frequencies above 3 kHz, although without preserving the exact temporal structure of the stimulus: the asymmetric displacement-receptor current function of the hair cell bundle is filtered by the cell's membrane time constant to produce a tonic depolarization of the soma, augmenting transmitter release and thus exciting VIIIth nerve terminals.

The high-speed demands of mechanoelectrical transduction have resulted in some impressive ionic specializations within the inner ear. An unusual adaptation of the hair cell in this regard is that K^+ serves both to depolarize *and* repolarize the cell, enabling the hair cell's K^+ gradient to be largely maintained by passive ion movement alone. As with other epithelial cells, the basal and apical surfaces of the hair cell are separated by tight junctions, allowing separate extracellular ionic environments at these two surfaces. The apical end (including the stereocilia) protrudes into the scala media and is exposed to the K^+-rich, Na^+-poor **endolymph**, which is produced by dedicated ion pumping cells in the **stria vascularis** (Figure 12.10). The basal end of the hair cell body is bathed in the same fluid that fills the scala tympani, the perilymph, which resembles other extracellular fluids in that it is K^+-poor and Na^+-rich. In addition, the compartment containing endolymph is about 80 mV more positive than the perilymph compartment (this difference is known as the endocochlear potential), while the inside of the hair cell is about 45 mV more negative than the perilymph (and 125 mV more negative than the endolymph). The resulting electrical gradient across the membrane of the stereocilia (about 125 mV; the difference between the hair cell resting potential and the endocochlear potential) drives K^+ through open transduc-

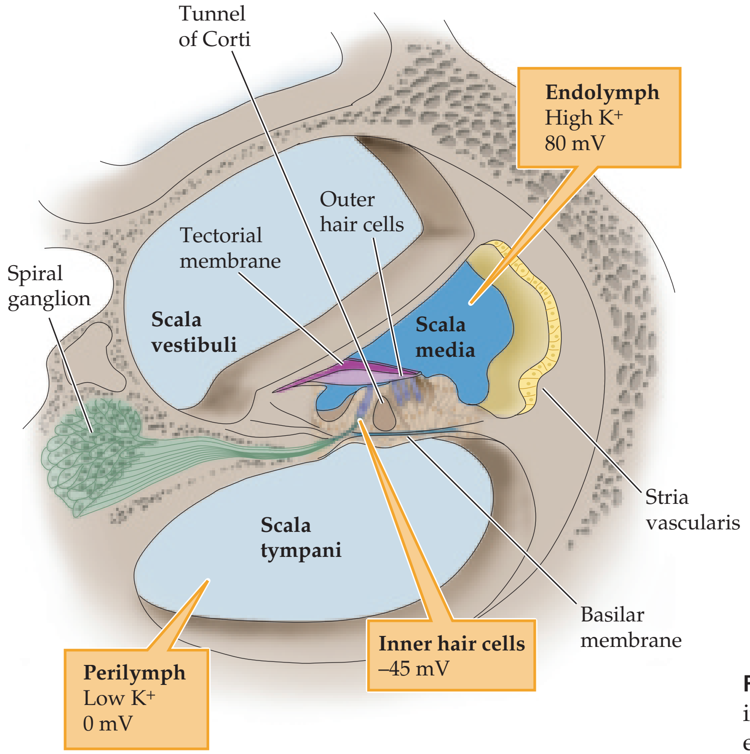


Figure 12.10 The stereocilia of the hair cells protrude into the endolymph, which is high in K^+ and has an electrical potential of +80 mV relative to the perilymph.

tion channels into the hair cell, even though these cells already have a high internal K^+ concentration. K^+ entry via the transduction channels electrotonically depolarizes the hair cell, opening voltage-gated Ca^{2+} and K^+ channels located in the membrane of the hair cell soma (see Box B in Chapter 13). The opening of *somatic* K^+ channels favors K^+ efflux, and thus repolarization; the efflux occurs because the perilymph surrounding the basal end is low in K^+ relative to the cytosol, and because the equilibrium potential for K^+ is more negative than the hair cell's resting potential ($E_{KBasal} \approx -85$ mV). Repolarization of the hair cell via K^+ efflux is also facilitated by Ca^{2+} entry. In addition to modulating the release of neurotransmitter, Ca^{2+} entry opens Ca^{2+}-dependent K^+ channels, which provide another avenue for K^+ to enter the perilymph. Indeed, the interaction of Ca^{2+} influx and Ca^{2+}-dependent K^+ efflux can lead to electrical resonances that enhance the tuning of response properties within the inner ear (also explained in Box B in Chapter 13). In essence, the hair cell operates as two distinct compartments, each dominated by its own Nernst equilibrium potential for K^+; this arrangement ensures that the hair cell's ionic gradient does not run down, even during prolonged stimulation. At the same time, rupture of Reissner's membrane, which normally separates the scalae media and vestibuli, or compounds such as ethacrynic acid (see Box A), which selectively poison the ion-pumping cells of the stria vascularis, can cause the endocochlear potential to dissipate, resulting in a sensorineural hearing deficit. In short, the hair cell exploits the different ionic milieus of its apical and basal surfaces to provide extremely fast and energy-efficient repolarization.

Two Kinds of Hair Cells in the Cochlea

The cochlear hair cells in humans consist of one row of **inner hair cells** and three rows of **outer hair cells** (see Figure 12.4). The inner hair cells are the actual sensory receptors, and 95% of the fibers of the auditory nerve that project to the brain arise from this subpopulation. The terminations on the outer hair cells are almost all from efferent axons that arise from cells in the superior olivary complex.

A clue to the significance of this efferent pathway was provided by the discovery that an active process within the cochlea, as mentioned, influences basilar membrane motion. First, it was found that the cochlea actually emits sound under certain conditions. These otoacoustical emissions can be detected by placing a sensitive microphone at the eardrum and monitoring the response after briefly presenting a tone or click, and provide a useful means to assess cochlear function in the newborn (this test is now done routinely to rule out congenital deafness). Such emissions can also occur spontaneously, especially in certain pathological states, and are thus one potential source of **tinnitus** (ringing in the ears). These observations clearly indicate that a process within the cochlea is capable of producing sound. Second, stimulation of the crossed olivocochlear bundle, which supplies efferent input to the outer hair cells, can broaden VIIIth nerve tuning curves. Third, the high sensitivity notch of VIIIth nerve tuning curves is lost when the outer hair cells are selectively inactivated. Finally, isolated outer hair cells contract and expand in response to small electrical currents, thus providing a potential source of energy to drive an active process within the cochlea. Thus, it seems likely that the outer hair cells sharpen the frequency-resolving power of the cochlea by actively contracting and relaxing, thus changing the stiffness of the tectorial membrane at particular locations. This active process explains the nonlinear vibration of the basilar membrane at low sound intensities (see Box D).

Tuning and Timing in the Auditory Nerve

The rapid response time of the transduction apparatus allows the membrane potential of the hair cell to follow deflections of the hair bundle up to moderately high frequencies of oscillation. In humans, the receptor potentials of certain hair cells and the action potentials of their associated auditory nerve fiber can follow stimuli of up to about 3 kHz in a one-to-one fashion. Such real-time encoding of stimulus frequency by the pattern of action potentials in the auditory nerve is known as the "volley theory" of auditory information transfer. Even these extraordinarily rapid processes, however, fail to follow frequencies above 3 kHz (see Figure 12.9). Accordingly, some other mechanism must be used to transmit auditory information at higher frequencies. The tonotopically organized basilar membrane provides an alternative to temporal coding, namely a "labeled-line" coding mechanism. In this case, frequency information is specified by preserving the tonotopy of the cochlea at higher levels in the auditory pathway. Because the auditory nerve fibers associate with the inner hair cells in approximately a one-to-one ratio (although several or more VIIIth nerve fibers synapse on a single hair cell), each auditory nerve fiber transmits information about only a small part of the audible frequency spectrum. As a result, auditory nerve fibers related to the apical end of the cochlea respond to low frequencies, and fibers that are related to the basal end respond to high frequencies (see Figure 12.5). The limitations of specific fibers can be seen in electrophysiological recordings of responses to sound (Figure 12.11). These threshold functions are called **tuning curves**, and the lowest threshold of the tuning curve is called the **characteristic frequency**. Since the topographical order of the characteristic frequency of neurons is retained throughout the system, information about frequency is also preserved. Cochlear implants (see Box C) exploit the tonotopic organization of the cochlea, and particularly its eighth nerve afferents, to roughly recreate the patterns of VIIIth nerve activity elicited by sounds. In patients with damaged hair cells, such implants can effectively bypass the impaired transduction apparatus, and thus restore some degree of auditory function.

The other prominent feature of hair cells—their ability to follow the waveform of low-frequency sounds—is also important in other more subtle aspects of auditory coding. As mentioned earlier, hair cells have biphasic response properties. Because hair cells release transmitter only when depolarized, auditory nerve fibers fire only during the positive phases of low-frequency sounds (see Figure 12.11). The resultant "phase locking" that results provides temporal information from the two ears to neural centers that compare interaural time differences. The evaluation of interaural time differences provides a critical cue for sound localization and the perception of auditory "space." That auditory space can be perceived is remarkable, given that the cochlea, unlike the retina, cannot represent space directly. A final point is that VIIIth nerve activity patterns are not simply faithful neural replicas of the auditory stimulus itself. Indeed, William Bialek and his colleagues at Princeton University have shown that the VIIIth nerve in the bullfrog encodes conspecific mating calls more efficiently than artificial sounds with similar frequency and amplitude characteristics. Thus both animal and human studies support the idea that the auditory periphery is optimized to

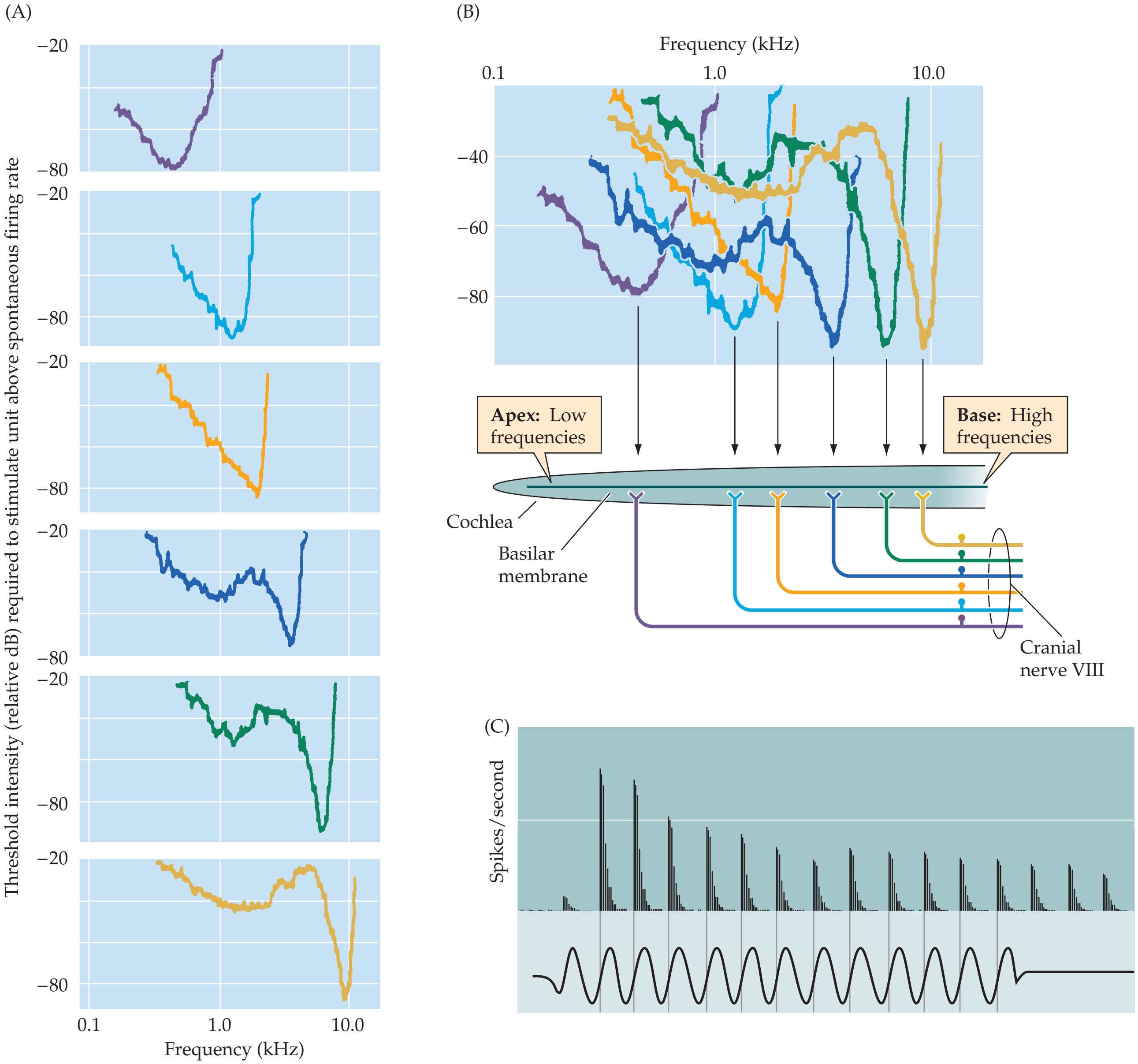


Figure 12.11 Response properties of auditory nerve fibers. (A) Frequency tuning curves of six different fibers in the auditory nerve. Each graph plots, across all frequencies to which the fiber responds, the minimum sound level required to increase the fiber's firing rate above its spontaneous firing level. The lowest point in the plot is the weakest sound intensity to which the neuron will respond. The frequency at this point is called the neuron's characteristic frequency. (B) The frequency tuning curves of auditory nerve fibers superimposed and aligned with their approximate relative points of innervation along the basilar membrane. (In the side view schematic, the basilar membrane is represented as a black line within the unrolled cochlea.) (C) Temporal response patterns of a low-frequency axon in the auditory nerve. The stimulus waveform is indicated beneath the histograms, which show the phase-locked responses to a 50-ms tone pulse of 260 Hz. Note that the spikes are all timed to the same phase of the sinusoidal stimulus. (A after Kiang and Moxon, 1972; C after Kiang, 1984.)

transmit species-typical vocal sounds, rather than simply transmitting all sounds equally well to central auditory areas.

How Information from the Cochlea Reaches Targets in the Brainstem

A hallmark of the ascending auditory system is its parallel organization. This arrangement becomes evident as soon as the auditory nerve enters the brainstem, where it branches to innervate the three divisions of the cochlear nucleus. The auditory nerve (the major component of cranial nerve VIII) comprises the central processes of the bipolar spiral ganglion cells in the cochlea (see Figure 12.4); each of these cells sends a peripheral process to contact one inner hair cell and a central process to innervate the cochlear nucleus. Within the cochlear nucleus, each auditory nerve fiber branches, sending an ascending branch to the anteroventral cochlear nucleus and a descending branch to the posteroventral cochlear nucleus and the dorsal cochlear nucleus (Figure 12.12). The tonotopic organization of the cochlea is maintained in the three parts of the cochlear nucleus, each of which contains different populations of cells with quite different properties. In addition, the patterns of termination of the auditory nerve axons differ in density and type; thus, there are several opportunities at this level for transformation of the information from the hair cells.

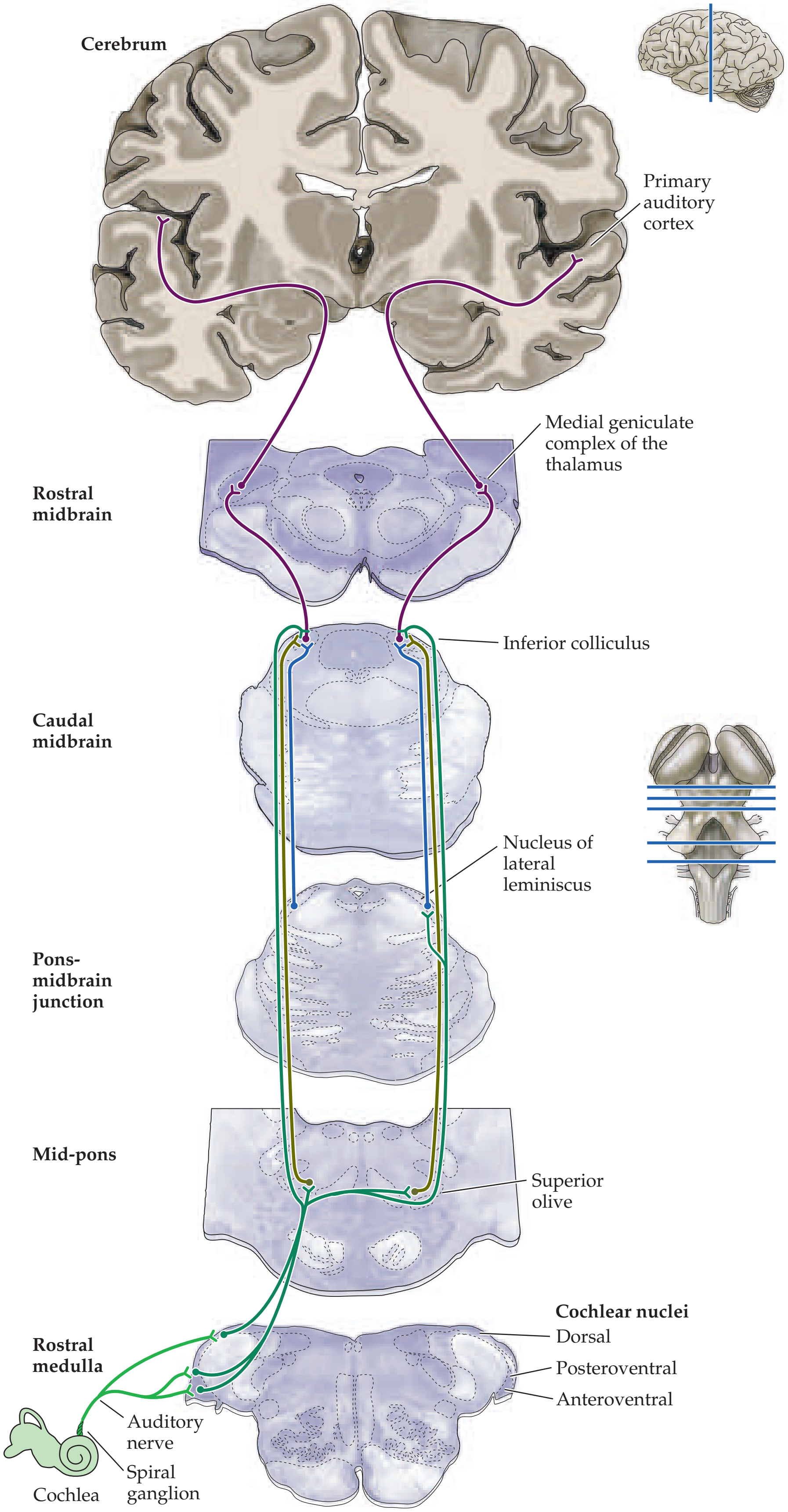
Integrating Information from the Two Ears

Just as the auditory nerve branches to innervate several different targets in the cochlear nuclei, the neurons in these nuclei give rise to several different pathways (see Figure 12.12). One clinically relevant feature of the ascending projections of the auditory brainstem is a high degree of bilateral connectivity, which means that damage to central auditory structures is almost never manifested as a monaural hearing loss. Indeed, monaural hearing loss strongly implicates unilateral peripheral damage, either to the middle or inner ear, or to the VIIIth nerve itself (see Box C). Given the relatively byzantine organization already present at the level of the auditory brainstem, it is useful to consider these pathways in the context of their functions.

The best-understood function mediated by the auditory brainstem nuclei, and certainly the one most intensively studied, is sound localization. Humans use at least two different strategies to localize the horizontal position of sound sources, depending on the frequencies in the stimulus. For frequencies below 3 kHz (which can be followed in a phase-locked manner), interaural *time* differences are used to localize the source; above these frequencies, interaural *intensity* differences are used as cues. Parallel pathways originating from the cochlear nucleus serve each of these strategies for sound localization.

The human ability to detect interaural time differences is remarkable. The longest interaural time differences, which are produced by sounds arising directly lateral to one ear, are on the order of only 700 microseconds (a value given by the width of the head divided by the speed of sound in air, about 340 m/s). Psychophysical experiments show that humans can actually detect interaural time differences as small as 10 microseconds; two sounds presented through earphones separated by such small interaural time differences are perceived as arising from the side of the leading ear. This sensitivity translates into accuracy for sound localization of about 1 degree.

Figure 12.12 Diagram of the major auditory pathways. Although many details are missing from this diagram, two important points are evident: (1) the auditory system entails several parallel pathways, and (2) information from each ear reaches both sides of the system, even at the level of the brainstem.


Cerebrum
Primary auditory cortex
Medial geniculate complex of the thalamus
Rostral midbrain
Inferior colliculus
Caudal midbrain
Nucleus of lateral leminiscus
Pons-midbrain junction
Mid-pons
Superior olive
Cochlear nuclei
Dorsal
Posteroventral
Anteroventral
Rostral medulla
Auditory nerve
Spiral ganglion
Cochlea

How is timing in the 10 microseconds range accomplished by neural components that operate in the millisecond range? The neural circuitry that computes such tiny interaural time differences consists of binaural inputs to the **medial superior olive** (**MSO**) that arise from the right and left anteroventral cochlear nuclei (Figure 12.13; see also Figure 12.12). The medial superior olive contains cells with bipolar dendrites that extend both medially and laterally. The lateral dendrites receive input from the ipsilateral anteroventral cochlear nucleus, and the medial dendrites receive input from the contralateral anteroventral cochlear nucleus (both inputs are excitatory). As might be expected, the MSO cells work as **coincidence detectors**, responding when both excitatory signals arrive at the same time. For a coincidence mechanism to be useful in localizing sound, different neurons must be maximally sensitive to different interaural time delays. The axons that project from the anteroventral cochlear nucleus evidently vary systematically in length to create delay lines. (Remember that the length of an axon divided by its conduction velocity equals the conduction time.) These anatomical differences compensate for sounds arriving at slightly different times at the two ears, so that the resultant neural impulses arrive at a particular MSO neuron simultaneously, making each cell especially sensitive to sound sources in a particular place. The mechanisms enabling MSO neurons to function as coincidence detectors at the microsecond level are still poorly understood, but certainly reflect one of the more impressive biophysical specializations in the nervous system.

Sound localization perceived on the basis of interaural time differences requires phase-locked information from the periphery, which, as already

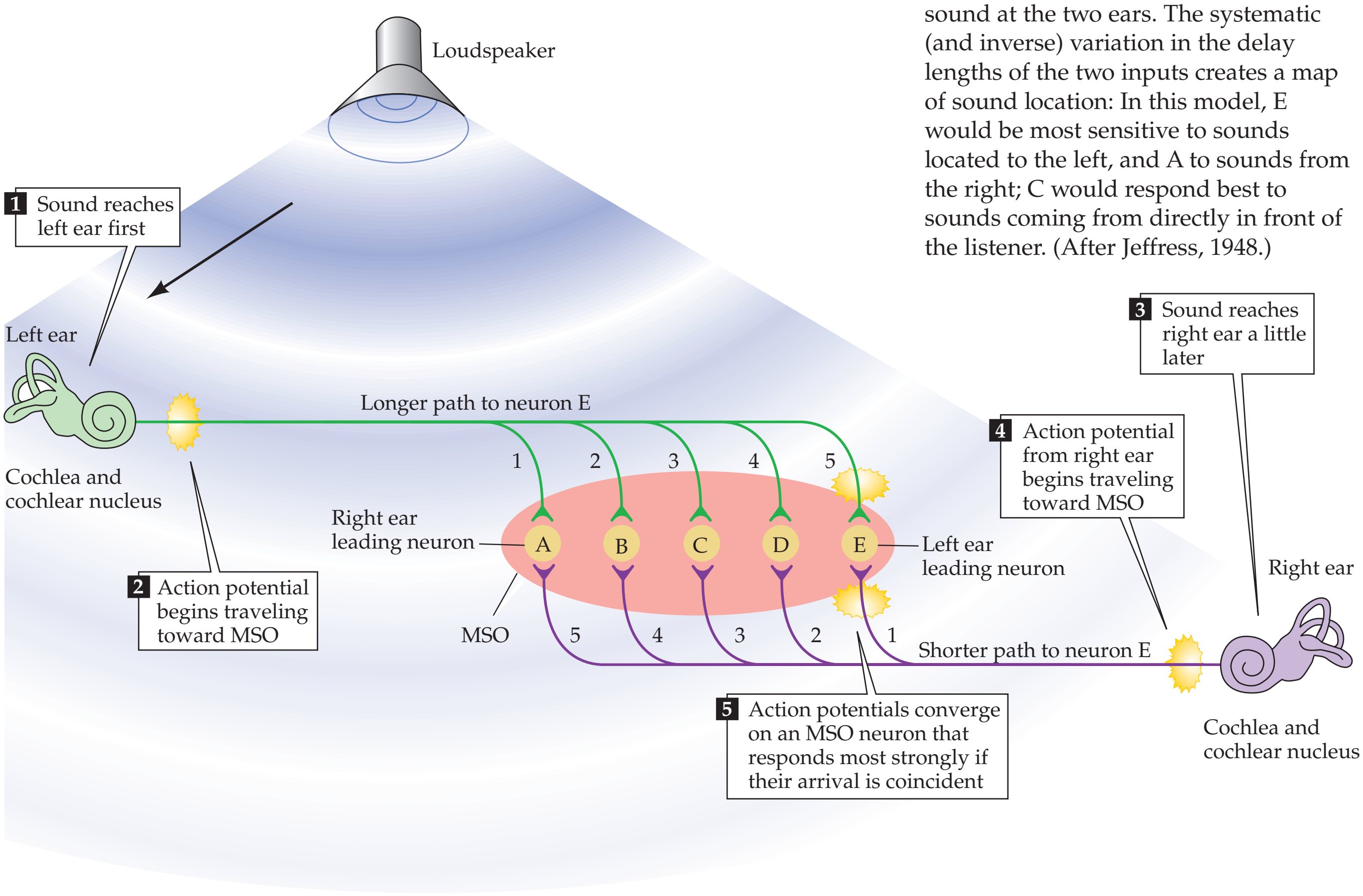

Loudspeaker
1 Sound reaches left ear first
Left ear
Cochlea and cochlear nucleus
2 Action potential begins traveling toward MSO
Longer path to neuron E
1
2
3
4
5
Right ear leading neuron
A
B
C
D
E
Left ear leading neuron
MSO
5
4
3
2
1
Shorter path to neuron E
3 Sound reaches right ear a little later
4 Action potential from right ear begins traveling toward MSO
Right ear
Cochlea and cochlear nucleus
5 Action potentials converge on an MSO neuron that responds most strongly if their arrival is coincident

Figure 12.13 Diagram illustrating how the MSO computes the location of a sound by interaural time differences. A given MSO neuron responds most strongly when the two inputs arrive simultaneously, as occurs when the contralateral and ipsilateral inputs precisely compensate (via their different lengths) for differences in the time of arrival of a sound at the two ears. The systematic (and inverse) variation in the delay lengths of the two inputs creates a map of sound location: In this model, E would be most sensitive to sounds located to the left, and A to sounds from the right; C would respond best to sounds coming from directly in front of the listener. (After Jeffress, 1948.)

emphasized, is available to humans only for frequencies below 3 kHz. (In barn owls, the reigning champions of sound localization, phase locking occurs at up to 9 kHz.) Therefore, a second mechanism must come into play at higher frequencies. At frequencies higher than about 2 kHz, the human head begins to act as an acoustical obstacle because the wavelengths of the sounds are too short to bend around it. As a result, when high-frequency sounds are directed toward one side of the head, an acoustical "shadow" of lower intensity is created at the far ear. These intensity differences provide a second cue about the location of a sound. The circuits that compute the position of a sound source on this basis are found in the **lateral superior olive** (**LSO**) and the **medial nucleus of the trapezoid body** (**MNTB**) (Figure 12.14). Excitatory axons project directly from the ipsilateral anteroventral cochlear nucleus to the LSO (as well as to the MSO; see Figure 12.13). Note that the LSO also receives inhibitory input from the contralateral ear, via an inhibitory neuron in the MNTB. This excitatory/inhibitory interaction

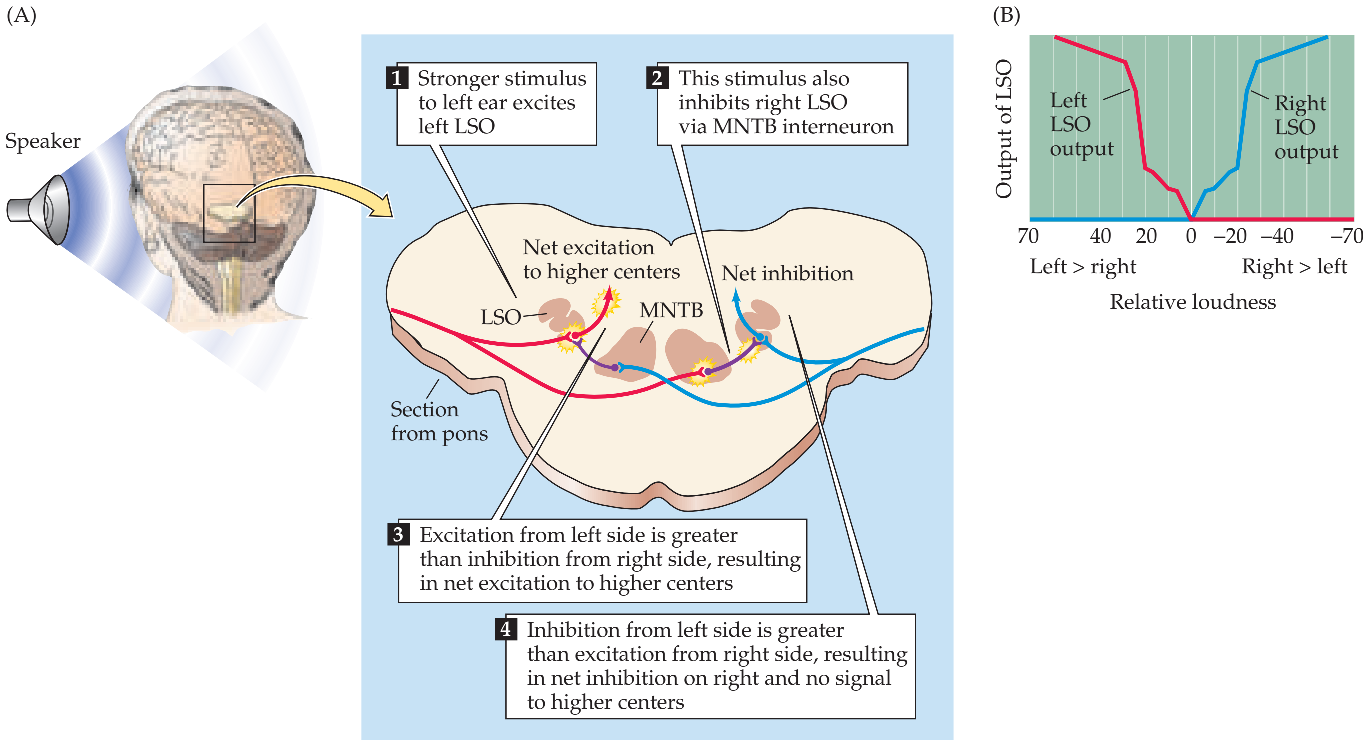

(A)
Speaker
1 Stronger stimulus to left ear excites left LSO
2 This stimulus also inhibits right LSO via MNTB interneuron
Net excitation to higher centers
Net inhibition
LSO
MNTB
Section from pons
3 Excitation from left side is greater than inhibition from right side, resulting in net excitation to higher centers
4 Inhibition from left side is greater than excitation from right side, resulting in net inhibition on right and no signal to higher centers
(B)
Output of LSO
Left LSO output
Right LSO output
70
40
20
0
−20
−40
−70
Left > right
Right > left
Relative loudness

Figure 12.14 Lateral superior olive neurons encode sound location through interaural intensity differences. (A) LSO neurons receive direct excitation from the ipsilateral cochlear nucleus; input from the contralateral cochlear nucleus is relayed via inhibitory interneurons in the MNTB. (B) This arrangement of excitation–inhibition makes LSO neurons fire most strongly in response to sounds arising directly lateral to the listener on the same side as the LSO, because excitation from the ipsilateral input will be great and inhibition from the contralateral input will be small. In contrast, sounds arising from in front of the listener, or from the opposite side, will silence the LSO output, because excitation from the ipsilateral input will be minimal, but inhibition driven by the contralateral input will be great. Note that LSOs are paired and bilaterally symmetrical; each LSO only encodes the location of sounds arising on the same side of the body as its location.

results in a net excitation of the LSO on the same side of the body as the sound source. For sounds arising directly lateral to the listener, firing rates will be highest in the LSO on that side; in this circumstance, the excitation via the ipsilateral anteroventral cochlear nucleus will be maximal, and inhibition from the contralateral MNTB minimal. In contrast, sounds arising closer to the listener's midline will elicit lower firing rates in the ipsilateral LSO because of increased inhibition arising from the contralateral MNTB. For sounds arising at the midline, or from the other side, the increased inhibition arising from the MNTB is powerful enough to completely silence LSO activity. Note that each LSO only encodes sounds arising in the ipsilateral hemifield; it therefore takes both LSOs to represent the full range of horizontal positions.

In summary, there are two separate pathways—and two separate mechanisms—for localizing sound. Interaural time differences are processed in the medial superior olive, and interaural intensity differences are processed in the lateral superior olive. These two pathways are eventually merged in the midbrain auditory centers.

Monaural Pathways from the Cochlear Nucleus to the Lateral Lemniscus

The binaural pathways for sound localization are only part of the output of the cochlear nucleus. This fact is hardly surprising, given that auditory perception involves much more than locating the position of the sound source. A second major set of pathways from the cochlear nucleus bypasses the superior olive and terminates in the **nuclei of the lateral lemniscus** on the contralateral side of the brainstem (see Figure 12.12). These particular pathways respond to sound arriving at one ear only and are thus referred to as monaural. Some cells in the lateral lemniscus nuclei signal the onset of sound, regardless of its intensity or frequency. Other cells in the lateral lemniscus nuclei process other temporal aspects of sound, such as duration. The precise role of these pathways in processing temporal features of sound is not yet known. As with the outputs of the superior olivary nuclei, the pathways from the nuclei of the lateral lemniscus converge at the midbrain.

Integration in the Inferior Colliculus

Auditory pathways ascending via the olivary and lemniscal complexes, as well as other projections that arise directly from the cochlear nucleus, project to the midbrain auditory center, the **inferior colliculus**. In examining how integration occurs in the inferior colliculus, it is again instructive to turn to the most completely analyzed auditory mechanism, the binaural system for localizing sound. As already noted, space is not mapped on the auditory receptor surface; thus the perception of auditory space must somehow be synthesized by circuitry in the lower brainstem and midbrain. Experiments in the barn owl, an extraordinarily proficient animal at localizing sounds, show that the convergence of binaural inputs in the midbrain produces something entirely new relative to the periphery—namely, a computed topographical representation of auditory space. Neurons within this **auditory space map** in the colliculus respond best to sounds originating in a specific region of space and thus have both a preferred elevation and a preferred horizontal location, or azimuth. Although comparable maps of auditory space have not yet been found in mammals, humans have a clear perception of both the elevational and azimuthal components of a sound's location, suggesting that we have a similar auditory space map.

Another important property of the inferior colliculus is its ability to process sounds with complex temporal patterns. Many neurons in the inferior colliculus respond only to frequency-modulated sounds, while others respond only to sounds of specific durations. Such sounds are typical components of biologically relevant sounds, such as those made by predators, or intraspecific communication sounds, which in humans include speech.

The Auditory Thalamus

Despite the parallel pathways in the auditory stations of the brainstem and midbrain, the **medial geniculate complex** (**MGC**) in the thalamus is an obligatory relay for all ascending auditory information destined for the cortex (see Figure 12.12). Most input to the MGC arises from the inferior colliculus, although a few auditory axons from the lower brainstem bypass the inferior colliculus to reach the auditory thalamus directly. The MGC has several divisions, including the ventral division, which functions as the major thalamocortical relay, and the dorsal and medial divisions, which are organized like a belt around the ventral division.

In some mammals, the strictly maintained tonotopy of the lower brainstem areas is exploited by convergence onto MGC neurons, generating specific responses to certain spectral combinations. The original evidence for this statement came from research on the response properties of cells in the MGC of echolocating bats. Some cells in the so-called belt areas of the bat MGC respond only to combinations of widely spaced frequencies that are specific components of the bat's echolocation signal and of the echoes that are reflected from objects in the bat's environment. In the mustached bat, where this phenomenon has been most thoroughly studied, the echolocation pulse has a changing frequency (frequency-modulated, or FM) component that includes a fundamental frequency and one or more harmonics. The fundamental frequency (FM_1) has low intensity and sweeps from 30 kHz to 20 kHz. The second harmonic (FM_2) is the most intense component and sweeps from 60 kHz to 40 kHz. Note that these frequencies do not overlap. Most of the echoes are from the intense FM_2 sound, and virtually none arise from the weak FM_1, even though the emitted FM_1 is loud enough for the bat to hear. Apparently, the bat assesses the distance to an object by measuring the delay between the FM_1 emission and the FM_2 echo. Certain MGC neurons respond when FM_2 follows FM_1 by a specific delay, providing a mechanism for sensing such frequency combinations. Because each neuron responds best to a particular delay, the population of MGC neurons encodes a range of distances.

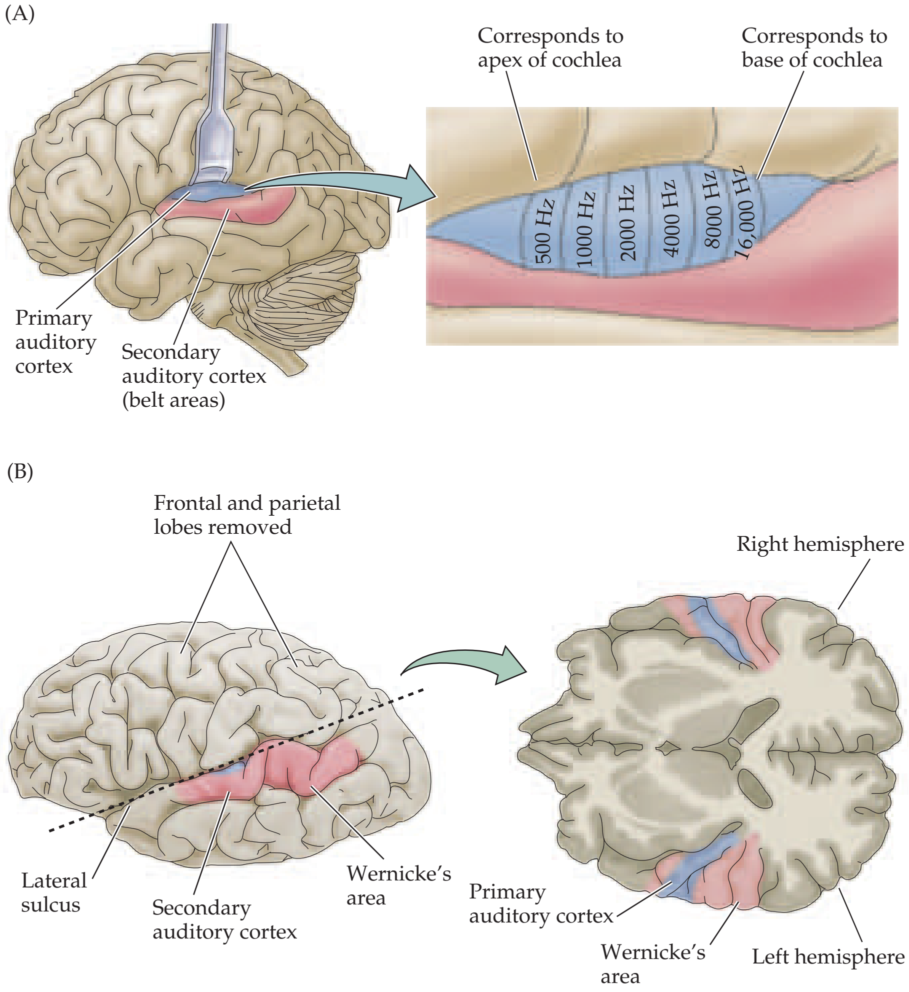
Bat sonar illustrates two important points about the function of the auditory thalamus. First, the MGC is the first station in the auditory pathway where selectivity for combinations of frequencies is found. The mechanism responsible for this selectivity is presumably the ultimate convergence of inputs from cochlear areas with different spectral sensitivities. Second, cells in the MGC are selective not only for frequency combinations, but also for specific time intervals between the two frequencies. The principle is the same as that described for binaural neurons in the medial superior olive, but in this instance, two monaural signals with different frequency sensitivity coincide, and the time difference is in the millisecond rather than the microsecond range.

In summary, neurons in the medial geniculate complex receive convergent inputs from spectrally and temporally separate pathways. This complex, by virtue of its convergent inputs, mediates the detection of specific spectral and temporal combinations of sounds. In many species, including humans, varying spectral and temporal cues are especially important features of communication sounds. It is not known whether cells in the human medial geniculate are selective to combinations of sounds, but the processing of speech certainly requires both spectral and temporal combination sensitivity.

The Auditory Cortex

The ultimate target of afferent auditory information is the auditory cortex. Although the auditory cortex has a number of subdivisions, a broad distinction can be made between a primary area and peripheral, or belt, areas. The **primary auditory cortex** (**A1**) is located on the superior temporal gyrus in the temporal lobe and receives point-to-point input from the ventral division of the medial geniculate complex; thus, it contains a precise tonotopic map. The **belt areas** of the auditory cortex receive more diffuse input from the belt areas of the medial geniculate complex and therefore are less precise in their tonotopic organization.

The primary auditory cortex (A1) has a topographical map of the cochlea (Figure 12.15), just as the primary visual cortex (V1) and the primary somatic sensory cortex (S1) have topographical maps of their respective sensory

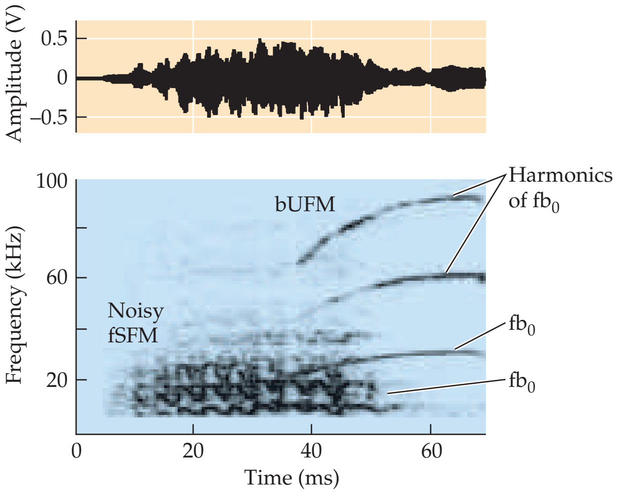

(A)
Corresponds to apex of cochlea
Corresponds to base of cochlea
500 Hz
1000 Hz
2000 Hz
4000 Hz
8000 Hz
16,000 Hz
Primary auditory cortex
Secondary auditory cortex (belt areas)
(B)
Frontal and parietal lobes removed
Right hemisphere
Lateral sulcus
Secondary auditory cortex
Wernicke's area
Primary auditory cortex
Wernicke's area
Left hemisphere

sylvius

Figure 12.15 The human auditory cortex. (A) Diagram showing the brain in left lateral view, including the depths of the lateral sulcus, where part of the auditory cortex occupying the superior temporal gyrus normally lies hidden. The primary auditory cortex (A1) is shown in blue; the surrounding belt areas of the auditory cortex are in red. The primary auditory cortex has a tonotopic organization, as shown in this blowup diagram of a segment of A1 (right). (B) Diagram of the brain in left lateral view, showing locations of human auditory cortical areas related to processing speech sounds in the intact hemisphere. *Right:* An oblique section (plane of dashed line) shows the cortical areas on the superior surface of the temporal lobe. Note that Wernicke's area, a region important in comprehending speech, is just posterior to the primary auditory cortex.

Box E

Representing Complex Sounds in the Brains of Bats and Humans



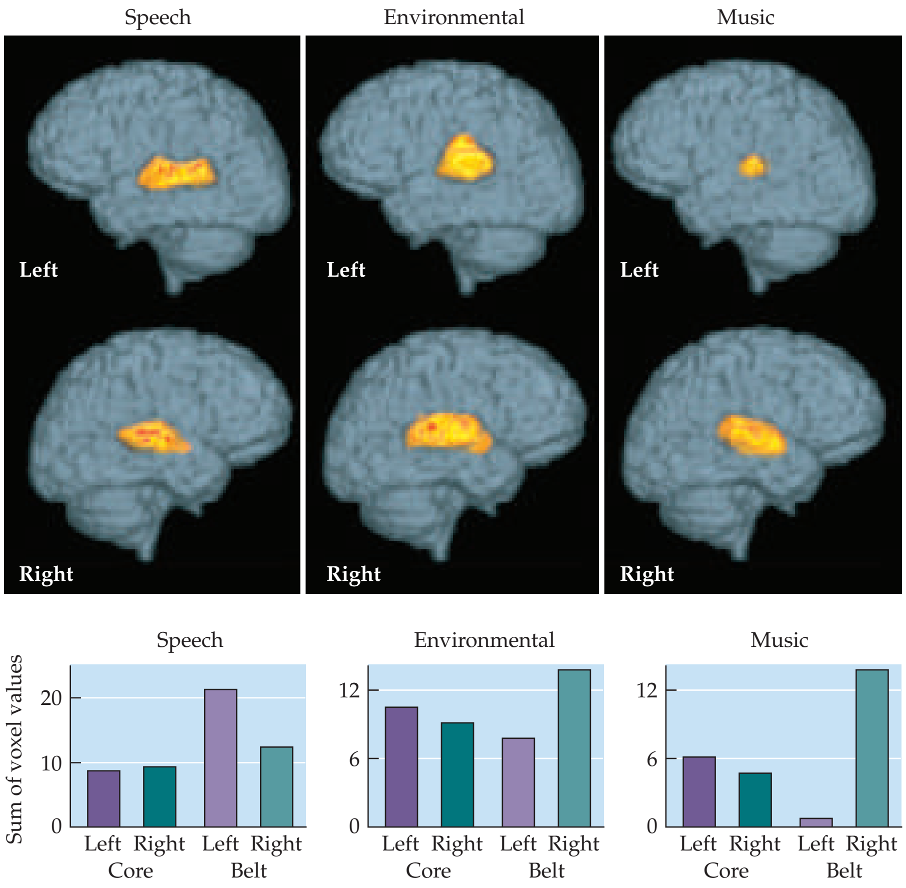
(A) Amplitude envelope (above) and spectrogram (below) of a composite syllable emitted by mustached bats for social communication. This composite consists of two simple syllables, a fixed Sinusoidal FM (fSFM) and a bent Upward FM (bUFM) that emerges from the fSFM after some overlap. Each syllable has its own fundamental (fa_0 and fb_0) and multiple harmonics. (Courtesy of Jagmeet Kanwal.)

Most natural sounds are complex, meaning that they differ from the pure tones or clicks that are frequently used in neurophysiological studies of the auditory system. Rather, natural sounds are tonal: they have a fundamental frequency that largely determines the "pitch" of the sound, and one or more harmonics of different intensities that contribute to the quality or "timbre" of a sound. The frequency of a harmonic is, by definition, a multiple of the fundamental frequency, and both may be modulated over time. Such *frequency-modulated* (FM) sweeps can rise or fall in frequency, or change in a sinusoidal or some other fashion. Occasionally, multiple nonharmonic frequencies may be simultaneously present in some communication or musical sounds. In some sounds, a level of spectral splatter or "broadband noise" is embedded within tonal or frequency modulated sounds. The variations in the sound spectrum are typically accompanied by a modulation of the amplitude envelop of the complex sound as well. All of these features can be visualized by performing a spectrographic analysis.

How does the brain represent such complex natural sounds? Cognitive studies of complex sound perception provide some understanding of how a large but limited number of neurons in the brain can dynamically represent an infinite variety of natural stimuli in the sensory environment of humans and other animals. In bats, specializations for processing complex sounds are apparent. Studies in echolocating bats show that both communication and echolocation sounds (Figure A) are processed not only within some of the same areas, but also within the same neurons in the auditory cortex. In humans, multiple modes of processing are also likely, given the large overlap within the superior and middle temporal gyri in the temporal lobe for the representation of different types of complex sounds.

Asymmetrical representation is another common principle of complex sound processing that results in lateralized (though largely overlapping) representations of natural stimuli. Thus, speech sounds that are important for communication are lateralized to the left in the belt regions of the auditory cortex, whereas environmental sounds that are important for reacting to and recogniz-

epithelia. Unlike the visual and somatic sensory systems, however, the cochlea has already decomposed the acoustical stimulus so that it is arrayed tonotopically along the length of the basilar membrane. Thus, A1 is said to comprise a tonotopic map, as do most of the ascending auditory structures between the cochlea and the cortex. Orthogonal to the frequency axis of the tonotopic map is a striped arrangement of binaural properties. The neurons in one stripe are excited by both ears (and are therefore called EE cells), while the neurons in the next stripe are excited by one ear and inhibited by the other ear (EI cells). The EE and EI stripes alternate, an arrangement that is reminiscent of the ocular dominance columns in V1 (see Chapter 11).



(B) *Top:* Reconstructed functional magnetic resonance images of BOLD contrast signal change (average for 8 subjects) showing significant ($p < 0.001$) activation elicited by speech, environmental, and musical sounds on surface views of the left versus the right side of the human brain. *Bottom:* Bar graphs showing the total significant activation to each category of complex sounds in the core and belt areas of the auditory cortex for the left versus the right side. (Courtesy of Jagmeet Kanwal.)

ing aspects of the auditory environment are represented in each hemisphere (Figure B). Musical sounds that can either motivate us to march in war or to relax and meditate when coping with physical and emotional stress are highly lateralized to the right in the belt regions of the auditory cortex. The extent of lateralization for speech and possibly music may vary with sex, age, and training. In some species of bats, mice, and primates, processing of natural communication sounds appears to be lateralized to the left hemisphere. In summary, natural sounds are complex and their representation within the sensory cortex tends to be asymmetric across the two hemispheres.

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The auditory cortex obviously does much more than provide a tonotopic map and respond differentially to ipsi- and contralateral stimulation. Although the sorts of sensory processing that occur in the auditory cortex are not well understood, they are likely to be important to higher-order processing of natural sounds, especially those used for communication (Box E; see also Chapter 26). One clue about such processing comes from work in marmosets, a small neotropical primate with a complex vocal repertoire. The primary auditory cortex and belt areas of these animals are indeed organized tonotopically, but also contain neurons that are strongly responsive to spectral combinations that characterize certain vocalizations. The responses of these neurons to the tonal stimuli do not accurately predict their responses to the spectral combinations, suggesting that, in accord with peripheral optimization, cortical processing is in part dedicated to detecting particular intraspecific vocalizations.

Another clue about the role of the primary auditory cortex in the processing of intraspecific communication sounds comes from work in echolocating bats. Consistent with the essential role that echolocation plays in the survival of these crepuscular animals, certain regions of the bat primary auditory cortex, like those described in the MGC, are tuned in a systematic manner to the delays between frequency modulated pulses and their echoes, thus providing information about target distance and velocity. These delay-tuned neurons can exhibit highly specific responses to intraspecific communication calls, suggesting that the same cortical neurons can serve these two distinct auditory functions (see Box E). Evidently the general ability of the mammalian auditory cortex to detect certain spectral and temporal combinations of natural sounds has been exploited in bats to serve sonar-mediated navigation, yielding these dual function neurons.

Many of the dually specialized neurons are categorized as “combination-sensitive” neurons, i.e., neurons that show a nonlinear increase in their response magnitude when presented with a combination of tones and/or noise bands in comparison to the total magnitude of the response elicited by presenting each sound element separately. Combination-sensitive neurons are tuned to more than one frequency and are specialized to recognize complex species-specific sounds and extract information that is critical for survival. This sensitivity to combinations of simple sound elements appears to be a universal property of neurons for the perception of complex sounds by many animal species, such as frogs, birds bats and nonhuman primates. Therefore, combination-sensitive neurons most likely partake in the recognition of complex sounds in the human auditory cortex as well.

Sounds that are especially important for intraspecific communication often have a highly ordered temporal structure. In humans, the best example of such time-varying signals is speech, where different phonetic sequences are perceived as distinct syllables and words (see Box A in Chapter 26). Behavioral studies in cats and monkeys show that the auditory cortex is especially important for processing temporal sequences of sound. If the auditory cortex is ablated in these animals, they lose the ability to discriminate between two complex sounds that have the same frequency components but which differ in temporal sequence. Thus, without the auditory cortex, monkeys cannot discriminate one conspecific communication sound from another. The physiological basis of such temporal sensitivity likely requires neurons that are sensitive to time-varying cues in communication sounds. Indeed, electrophysiological recordings from the primary auditory cortex of both marmosets and bats show that some neurons that respond to intraspecific communication sounds do not respond as strongly when the sounds are played in reverse, indicating sensitivity to the sounds’ temporal features. Studies of human patients with bilateral damage to the auditory cortex also reveal severe problems in processing the temporal order of sounds. It seems likely, therefore, that specific regions of the human auditory cortex are specialized for processing elementary speech sounds, as well as other temporally complex acoustical signals, such as music (Box B). Thus, Wernicke’s area, which is critical to the comprehension of human language, lies within the secondary auditory area (Figure 12.15; see also Chapter 26).

Summary

Sound waves are transmitted via the external and middle ear to the cochlea of the inner ear, which exhibits a traveling wave when stimulated. For high-frequency sounds, the amplitude of the traveling wave reaches a maximum at the base of the cochlea; for low-frequency sounds, the traveling wave reaches a maximum at the apical end. The associated motions of the basilar membrane are transduced primarily by the inner hair cells, while the basilar membrane motion is itself actively modulated by the outer hair cells. Damage to the outer or middle ear results in conductive hearing loss, while hair cell damage results in a sensorineural hearing deficit. The tonotopic organization of the cochlea is retained at all levels of the central auditory system. Projections from the cochlea travel via the eighth nerve to the three main divisions of the cochlear nucleus. The targets of the cochlear nucleus neurons include the superior olivary complex and nuclei of the lateral lemniscus, where the binaural cues for sound localization are processed. The inferior colliculus is the target of nearly all of the auditory pathways in the lower brainstem and carries out important integrative functions, such as processing sound frequencies and integrating the cues for localizing sound in space. The primary auditory cortex, which is also organized tonotopically, is essential for basic auditory functions, such as frequency discrimination and sound localization, and also plays an important role in processing of intraspecific communication sounds. The belt areas of the auditory cortex have a less strict tonotopic organization and also process complex sounds, such as those that mediate communication. In the human brain, the major speech comprehension areas are located in the zone immediately adjacent to the auditory cortex.

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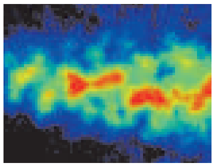
Chapter 13



The Vestibular System

Overview

The vestibular system has important sensory functions, contributing to the perception of self-motion, head position, and spatial orientation relative to gravity. It also serves important motor functions, helping to stabilize gaze, head, and posture. The peripheral portion of the vestibular system includes inner ear structures that function as miniaturized accelerometers and inertial guidance devices, continually reporting information about the motions and position of the head and body to integrative centers in the brainstem, cerebellum, and somatic sensory cortices. The central portion of the system includes the vestibular nuclei, which make extensive connections with brainstem and cerebellar structures. The vestibular nuclei also directly innervate motor neurons controlling extraocular, cervical, and postural muscles. This motor output is especially important to stabilization of gaze, head orientation, and posture during movement. Although we are normally unaware of its functioning, the vestibular system is a key component in postural reflexes and eye movements. Balance, gaze stabilization during head movement, and sense of orientation in space are all adversely affected if the system is damaged. These manifestations of vestibular damage are especially important in the evaluation of brainstem injury. Because the circuitry of the vestibular system extends through a large part of the brainstem, simple clinical tests of vestibular function can be performed to determine brainstem involvement, even on comatose patients.

The Vestibular Labyrinth

The main peripheral component of the vestibular system is an elaborate set of interconnected chambers—the **labyrinth**—that has much in common, and is in fact continuous with, the cochlea (see Chapter 12). Like the cochlea, the labyrinth is derived from the otic placode of the embryo, and it uses the same specialized set of sensory cells—hair cells—to transduce physical motion into neural impulses. In the cochlea, the motion is due to airborne sounds; in the labyrinth, the motions transduced arise from head movements, inertial effects due to gravity, and ground-borne vibrations (Box A).

The labyrinth is buried deep in the temporal bone and consists of the two **otolith organs** (the **utricle** and **saccule**) and three **semicircular canals** (Figure 13.1). The elaborate and tortuous architecture of these components explains why this part of the vestibular system is called the labyrinth. The utricle and saccule are specialized primarily to respond to *linear accelerations* of the head and *static head position relative to the graviational axis*, whereas the semicircular canals, as their shapes suggest, are specialized for responding to *rotational accelerations* of the head.

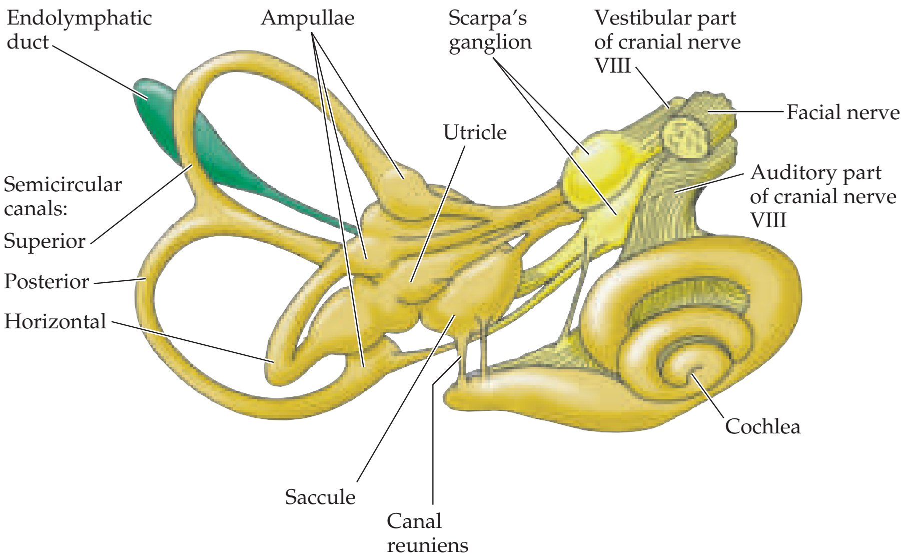


Figure 13.1 The labyrinth and its innervation. The vestibular and auditory portions of the eighth nerve are shown; the small connection from the vestibular nerve to the cochlea contains auditory efferent fibers. General orientation in head is shown in Figure 12.3; see also Figure 13.8.

The intimate relationship between the cochlea and the labyrinth goes beyond their common embryonic origin. Indeed, the cochlear and vestibular spaces are actually joined (see Figure 13.1), and the specialized ionic environments of the vestibular end organ parallel those of the cochlea. The membranous sacs within the bone are filled with fluid (endolymph) and are collectively called the membranous labyrinth. The endolymph (like the cochlear endolymph) is similar to intracellular solutions in that it is high in K^+ and low in Na^+. Between the bony walls (the osseous labyrinth) and the membranous labyrinth is another fluid, the perilymph, which is similar in composition to cerebrospinal fluid (i.e., low in K^+ and high in Na^+; see Chapter 12).

The vestibular hair cells are located in the utricle and saccule and in three juglike swellings called **ampullae**, located at the base of the semicircular canals next to the utricle. Within each ampulla, the vestibular hair cells extend their hair bundles into the endolymph of the membranous labyrinth. As in the cochlea, tight junctions seal the apical surfaces of the vestibular hair cells, ensuring that endolymph selectively bathes the hair cell bundle while remaining separate from the perilymph surrounding the basal portion of the hair cell.

Vestibular Hair Cells

The vestibular hair cells, which like cochlear hair cells transduce minute displacements into behaviorally relevant receptor potentials, provide the basis for vestibular function. Vestibular and auditory hair cells are quite similar; a detailed description of hair cell structure and function has already been given in Chapter 12. As in the case of auditory hair cells, movement of the stereocilia toward the kinocilium in the vestibular end organs opens mechanically gated transduction channels located at the tips of the stereocilia, depolarizing the hair cell and causing neurotransmitter release onto (and excitation of) the vestibular nerve fibers. Movement of the stereocilia in the direction away from the kinocilium closes the channels, hyperpolarizing the hair cell and thus reducing vestibular nerve activity. The biphasic nature of the receptor potential means that some transduction channels are open in the absence of stimulation, with the result that hair cells tonically release transmitter, thereby generating considerable spontaneous activity in vestibular nerve fibers (see Figure 13.6). One consequence of these spontaneous action potentials is that the firing rates of vestibular fibers can increase or decrease in a manner that faithfully mimics the receptor potentials produced by the hair cells (Box B).

Importantly, the hair cell bundles in each vestibular organ have specific orientations (Figure 13.2). As a result, the organ as a whole is responsive to displacements in all directions. In a given semicircular canal, the hair cells in the ampulla are all polarized in the same direction. In the utricle and saccule, a specialized area called the **striola** divides the hair cells into two populations with opposing polarities (Figure 13.2C; see also Figure 13.4C). The directional polarization of the receptor surfaces is a basic principle of organization in the vestibular system, as will become apparent in the following descriptions of the individual vestibular organs.

The Otolith Organs: The Utricle and Saccule

Displacements and linear accelerations of the head, such as those induced by tilting or translational movements (see Box A), are detected by the two otolith organs: the saccule and the utricle. Both of these organs contain a

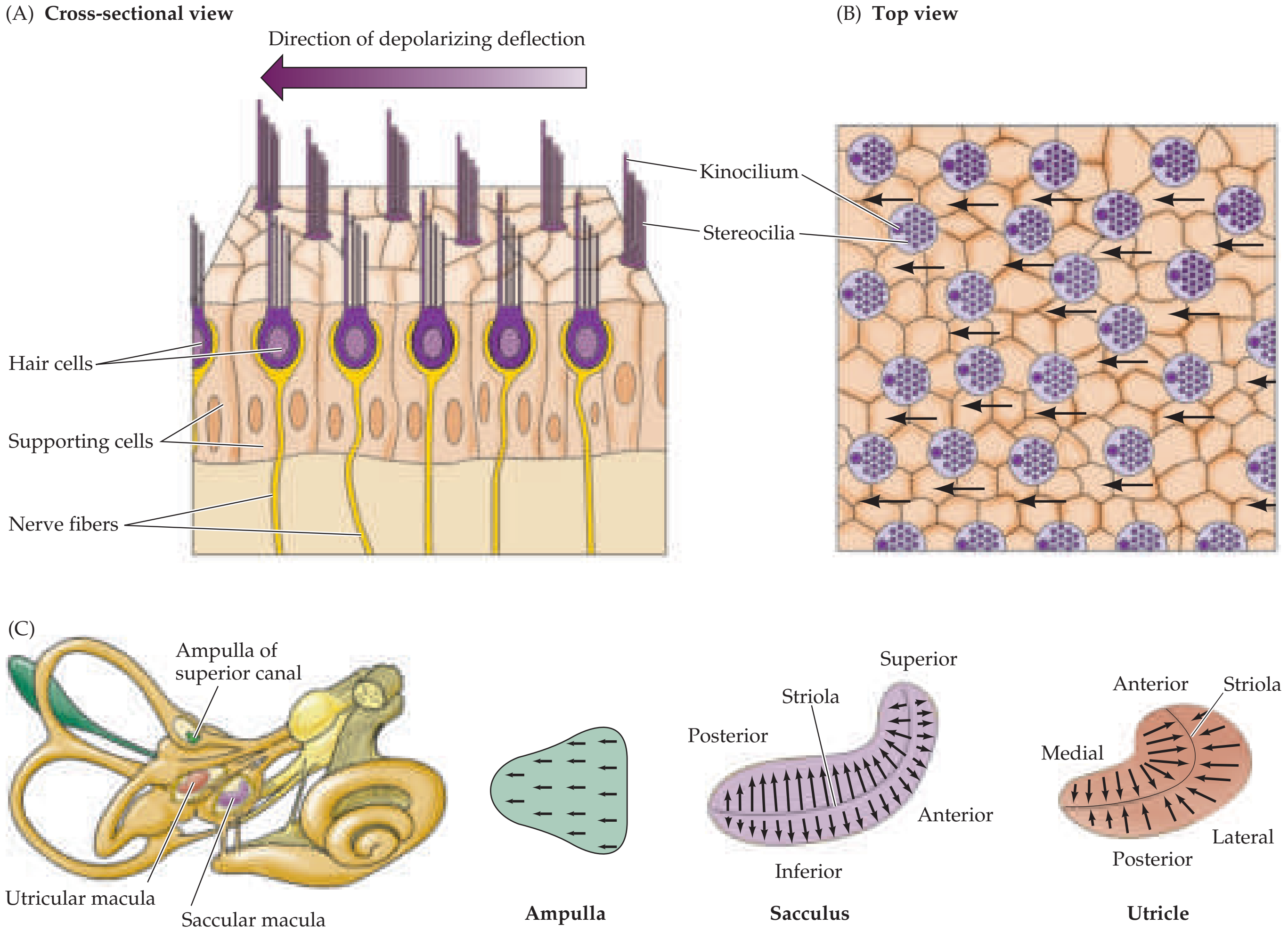
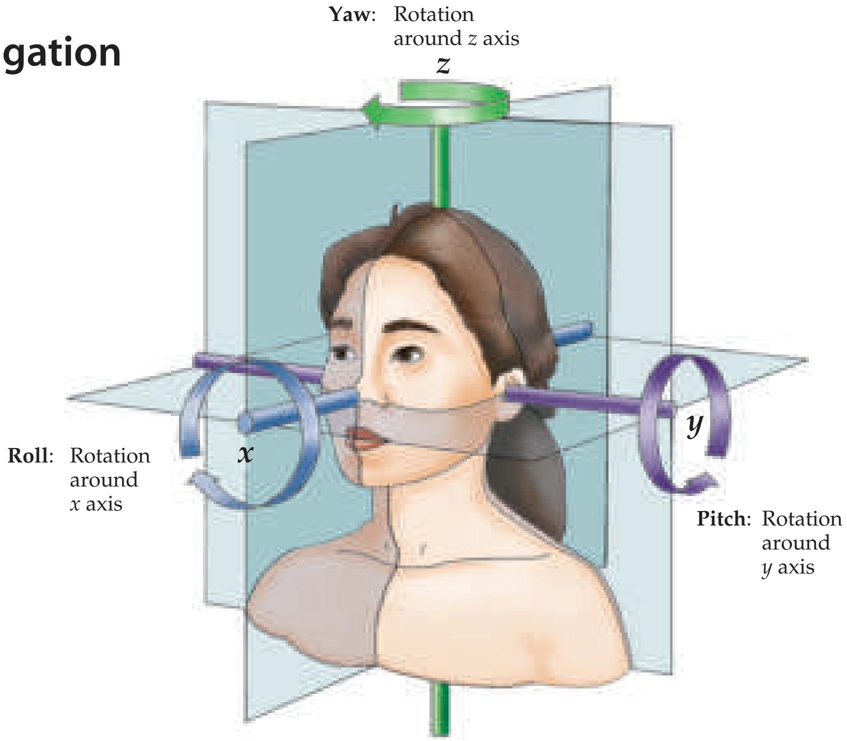

(A) Cross-sectional view
Direction of depolarizing deflection
Kinocilium
Stereocilia
Hair cells
Supporting cells
Nerve fibers
(B) Top view
(C)
Ampulla of superior canal
Utricular macula
Saccular macula
Ampulla
Superior
Striola
Posterior
Anterior
Inferior
Sacculus
Anterior
Striola
Medial
Lateral
Posterior
Utricle

Figure 13.2 The morphological polarization of vestibular hair cells and the polarization maps of the vestibular organs. (A) A cross section of hair cells shows that the kinocilia of a group of hair cells are all located on the same side of the hair cell. The arrow indicates the direction of deflection that depolarizes the hair cell. (B) View looking down on the hair bundles. (C) In the ampulla located at the base of each semicircular canal, the hair bundles are oriented in the same direction. In the sacculus and utricle, the striola divides the hair cells into populations with opposing hair bundle polarities.

Box A

A Primer on Vestibular Navigation

The function of the vestibular system can be simplified by remembering some basic terminology of classical mechanics. All bodies moving in a three-dimensional framework have six degrees of freedom: three of these are translational and three are rotational. The translational elements refer to linear movements in the *x*, *y*, and *z* axes (the horizontal and vertical planes). Translational motion in these planes (linear acceleration and static displacement of the head) is the primary concern of the otolith organs. The three degrees of rotational freedom refer to a body's rotation relative to the *x*, *y*, and *z* axes and are commonly referred to as *roll*, *pitch*, and *yaw*. The semicircular canals are primarily responsible for sensing rotational accelerations around these three axes.


Yaw: Rotation around *z* axis
z
Roll: Rotation around *x* axis
x
y
Pitch: Rotation around *y* axis

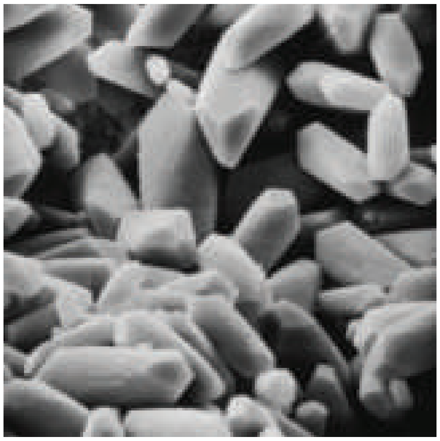


Figure 13.3 Scanning electron micrograph of calcium carbonate crystals (otoconia) in the utricular macula of the cat. Each crystal is about 50 mm long. (From Lindeman, 1973.)

sensory epithelium, the **macula**, which consists of hair cells and associated supporting cells. Overlying the hair cells and their hair bundles is a gelatinous layer; above this layer is a fibrous structure, the **otolithic membrane**, in which are embedded crystals of calcium carbonate called **otoconia** (Figures 13.3 and 13.4A). The crystals give the otolith organs their name (*otolith* is Greek for "ear stones"). The otoconia make the otolithic membrane considerably heavier than the structures and fluids surrounding it; thus, when the head tilts, gravity causes the membrane to shift relative to the sensory epithelium (Figure 13.4B). The resulting shearing motion between the otolithic membrane and the macula displaces the hair bundles, which are embedded in the lower, gelatinous surface of the membrane. This displacement of the hair bundles generates a receptor potential in the hair cells. A shearing motion between the macula and the otolithic membrane also occurs when the head undergoes linear accelerations (see Figure 13.5); the greater relative mass of the otolithic membrane causes it to lag behind the macula temporarily, leading to transient displacement of the hair bundle.

The similar effects exerted on otolithic hair cells by certain head tilts and linear accelerations would be expected to render these different stimuli perceptually equivalent when visual feedback is absent, as occurs in the dark or when the eyes are closed. Nevertheless, evidence suggests that subjects can discriminate between these two stimulus categories, apparently through combined activity of the otolith organs and the semicircular canals.

As already mentioned, the orientation of the hair cell bundles is organized relative to the striola, which demarcates the overlying layer of otoco-

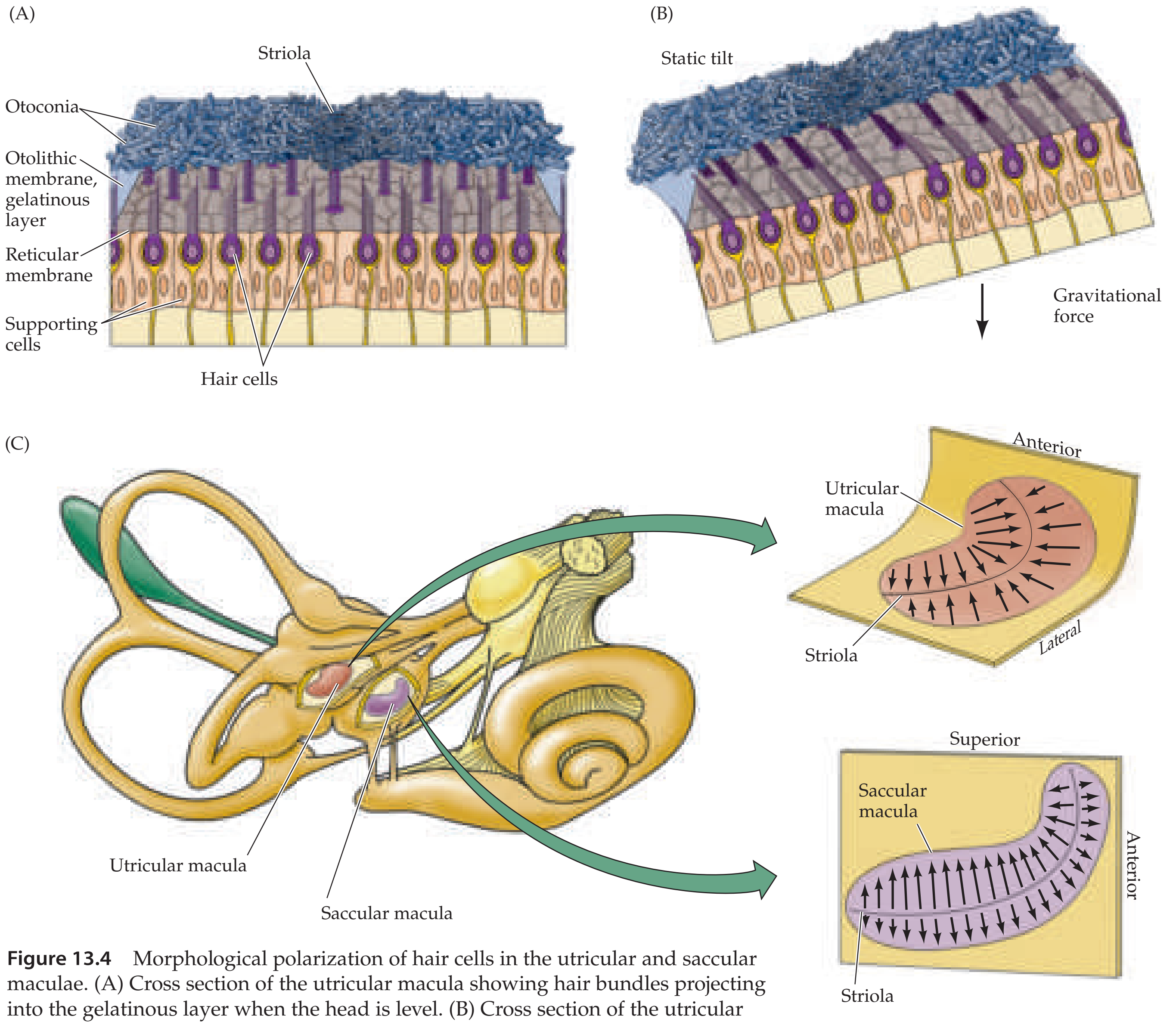

(A)
Striola
Otoconia
Otolithic membrane, gelatinous layer
Reticular membrane
Supporting cells
Hair cells
(B)
Static tilt
Gravitational force
(C)
Utricular macula
Saccular macula
Anterior
Utricular macula
Striola
Lateral
Superior
Saccular macula
Anterior
Striola

Figure 13.4 Morphological polarization of hair cells in the utricular and saccular maculae. (A) Cross section of the utricular macula showing hair bundles projecting into the gelatinous layer when the head is level. (B) Cross section of the utricular macula when the head is tilted. (C) Orientation of the utricular and saccular maculae in the head; arrows show orientation of the kinocilia, as in Figure 13.2. The *saccules* on either side are oriented more or less vertically, and the *utricles* more or less horizontally. The striola is a structural landmark consisting of small otoconia arranged in a narrow trench that divides each otolith organ. In the utricular macula, the kinocilia are directed toward the striola. In the saccular macula, the kinocilia point away from the striola. Note that, given the utricle and sacculus on both sides of the body, there is a continuous representation of all directions of body movement.

nia (see Figure 13.4A). The striola forms an axis of mirror symmetry such that hair cells on opposite sides of the striola have opposing morphological polarizations. Thus, a tilt along the axis of the striola will excite the hair cells on one side while inhibiting the hair cells on the other side. The saccular macula is oriented vertically and the utricular macula horizontally, with a continuous variation in the morphological polarization of the hair cells

Box B

Adaptation and Tuning of Vestibular Hair Cells

Hair Cell Adaptation

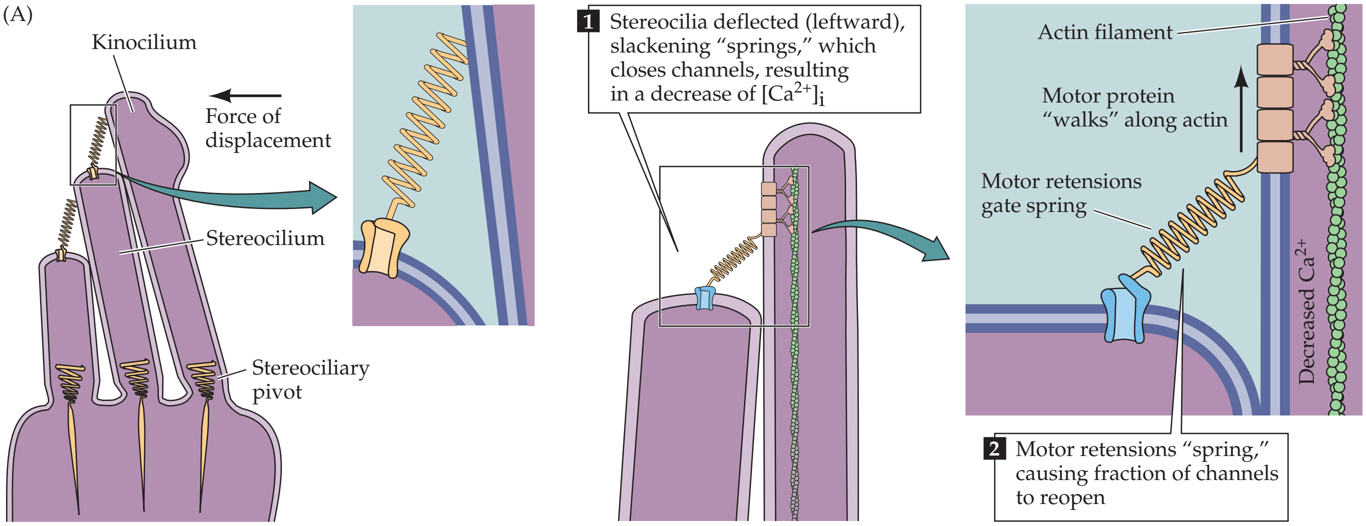
The minuscule movement of the hair bundle at sensory threshold has been compared to the displacement of the top of the Eiffel Tower by a thumb's breadth! Despite its great sensitivity, the hair cell can adapt quickly and continuously to static displacements of the hair bundle caused by large movements. Such adjustments are especially useful in the otolith organs, where adaptation permits hair cells to maintain sensitivity to small linear and angular accelerations of the head despite the constant input from gravitational forces that are over a million times greater. In other receptor cells, such as photoreceptors, adaptation is accomplished by regulating the second messenger cascade induced by the initial transduction event. The hair cell has to depend on a different strategy, however, because there is no second messenger system between the initial transduction event and the subsequent receptor potential (as might be expected for receptors that respond so rapidly).

Adaptation occurs in both directions in which the hair bundle displacement generates a receptor potential, albeit at different rates for each direction. When the hair bundle is pushed toward the kinocilium, tension is initially increased in the gating spring. During adaptation, tension decreases back to the resting level, perhaps because one end of the gating spring repositions itself along the shank of the stereocilium. When the hair bundle is displaced in the opposite direction, away from the kinocilium, tension in the spring initially decreases; adaptation then involves an increase in spring tension. One theory is that a calcium-regulated motor such as a myosin ATPase climbs along actin filaments in the stereocilium and actively resets the tension in the transduction spring. During sustained depolarization, some Ca^{2+} enters through the transduction channel, along with K^{+}. Ca^{2+} then causes the motor to spend a greater fraction of its time unbound from the actin, resulting in slippage of the spring down the side of the stereocilium. During sustained hyperpolarization (Figure A), Ca^{2+} levels drop below normal resting levels and the motor spends more of its time bound to the actin, thus climbing up the actin filaments and increasing the spring tension. As tension increases, some of the previously closed transduction channels open, admitting Ca^{2+} and thus slowing the motor's progress until a balance is struck between the climbing and slipping of the motor. In support of this model, when internal Ca^{2+} is reduced artificially, spring tension increases. This model of hair cell adaptation presents an elegant molecular solution to the regulation of a mechanical process.

Electrical Tuning

Although mechanical tuning plays an important role in generating frequency selectivity in the cochlea, there are other mechanisms that contribute to this process in vestibular and auditory nerve cells. These other tuning mechanisms are especially important in the otolith organs, where, unlike the cochlea, there are no

(A) Adaptation is explained in the gating spring model by adjustment of the insertion point of tips links. Movement of the insertion point up or down the shank of the stereocilium, perhaps driven by a Ca^{2+}-dependent protein motor, can continually adjust the resting tension of the tip link. (After Hudspeth and Gillespie, 1994.)


(A)
Kinocilium
Force of displacement
Stereocilium
Stereociliary pivot
Actin filament
Motor protein "walks" along actin
Motor retensions gate spring
Decreased Ca^{2+}

1 Stereocilia deflected (leftward), slackening "springs," which closes channels, resulting in a decrease of $[\mathrm{Ca}^{2+}]_i$

2 Motor retensions "spring," causing fraction of channels to reopen

obvious macromechanical resonances to selectively filter and/or enhance biologically relevant movements. One such mechanism is an electrical resonance displayed by hair cells in response to depolarization: The membrane potential of a hair cell undergoes damped sinusoidal oscillations at a specific frequency in response to the injection of depolarizing current pulses (Figure B).

The ionic mechanism of this process involves two major types of ion channels located in the membrane of the hair cell soma. The first of these is a voltage-activated Ca^{2+} conductance, which lets Ca^{2+} into the cell soma in response to depolarization, such as that generated by the transduction current. The second is a Ca^{2+}-activated K^+ conductance, which is triggered by the rise in internal Ca^{2+} concentration. These two currents produce an interplay of depolarization and repolarization that results in electrical resonance (Figure C). Activation of the hair cell's calcium-activated K^+ conductance occurs 10 to 100 times faster than that of similar currents in other cells. Such rapid kinetics allow this conductance to generate an electrical response that usually requires the fast properties of a voltage-gated channel.

Although a hair cell responds to hair bundle movement over a wide range of frequencies, the resultant receptor potential is largest at the frequency of electrical resonance. The resonance frequency represents the characteristic frequency of the hair cell, and transduction at that frequency will be most efficient. This electrical resonance has important implications for structures like the utricle and sacculus, which may encode a range of characteristic frequencies based on the different resonance frequencies of their constituent hair cells. Thus, electrical tuning in the otolith organs can generate enhanced tuning to biologically relevant frequencies of stimulation, even in the absence of macromechanical resonances within these structures.

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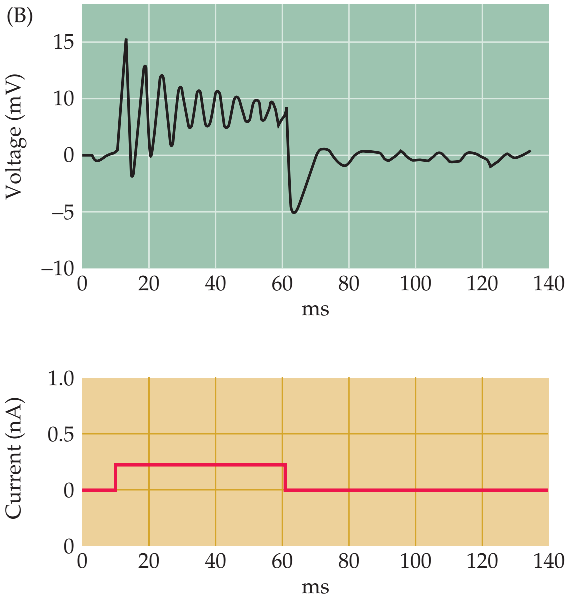
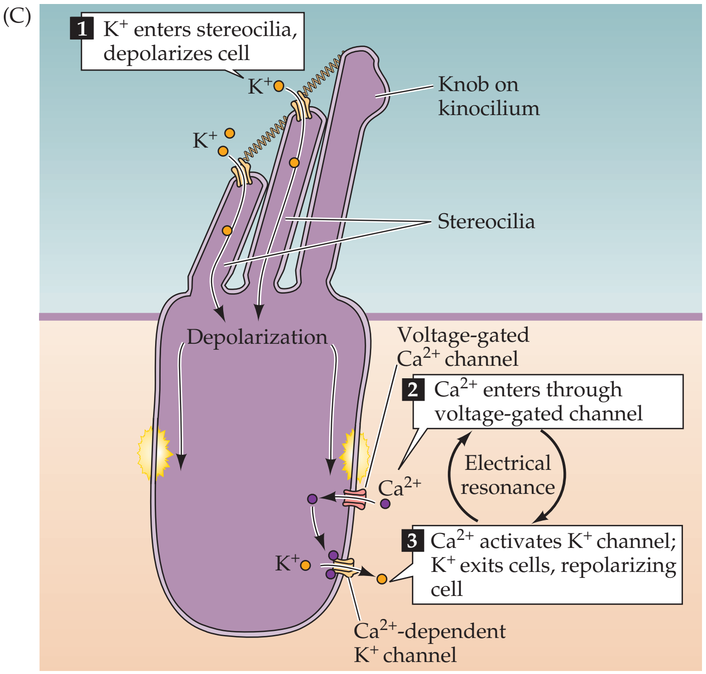


(B) Voltage oscillations (upper trace) in an isolated hair cell in response to a depolarizing current injection (lower trace). (After Lewis and Hudspeth, 1983.)


(C)
1 K⁺ enters stereocilia, depolarizes cell
K⁺
K⁺
Knob on kinocilium
Stereocilia
Depolarization
Voltage-gated Ca²⁺ channel
2 Ca²⁺ enters through voltage-gated channel
Electrical resonance
Ca²⁺
K⁺
3 Ca²⁺ activates K⁺ channel; K⁺ exits cells, repolarizing cell
Ca²⁺-dependent K⁺ channel

(C) Proposed ionic basis for electrical resonance in hair cells. (After Hudspeth, 1985.)

located in each macula (as shown in Figure 13.4C, where the arrows indicate the direction of movement that produces excitation). Inspection of the excitatory orientations in the maculae indicates that the utricle responds to movements of the head in the horizontal plane, such as sideways head tilts and rapid lateral displacements, whereas the saccule responds to movements in the vertical plane (up–down and forward–backward movements in the sagittal plane).

Note that the saccular and utricular maculae on one side of the head are mirror images of those on the other side. Thus, a tilt of the head to one side has opposite effects on corresponding hair cells of the two utricular maculae. This concept is important in understanding how the central connections of the vestibular periphery mediate the interaction of inputs from the two sides of the head (see the next section).

How Otolith Neurons Sense Linear Forces

The structure of the otolith organs enables them to sense both static displacements, as would be caused by tilting the head relative to the gravitational axis, and transient displacements caused by translational movements of the head. The mass of the otolithic membrane relative to the surrounding endolymph, as well as the otolithic membrane's physical uncoupling from the underlying macula, means that hair bundle displacement will occur transiently in response to linear accelerations and tonically in response to tilting of the head. Therefore, both tonic and transient information can be conveyed by these sense organs. Figure 13.5 illustrates some of the forces produced by head tilt and linear accelerations on the utricular macula.

These properties of hair cells are reflected in the responses of the vestibular nerve fibers that innervate the otolith organs. The nerve fibers have a

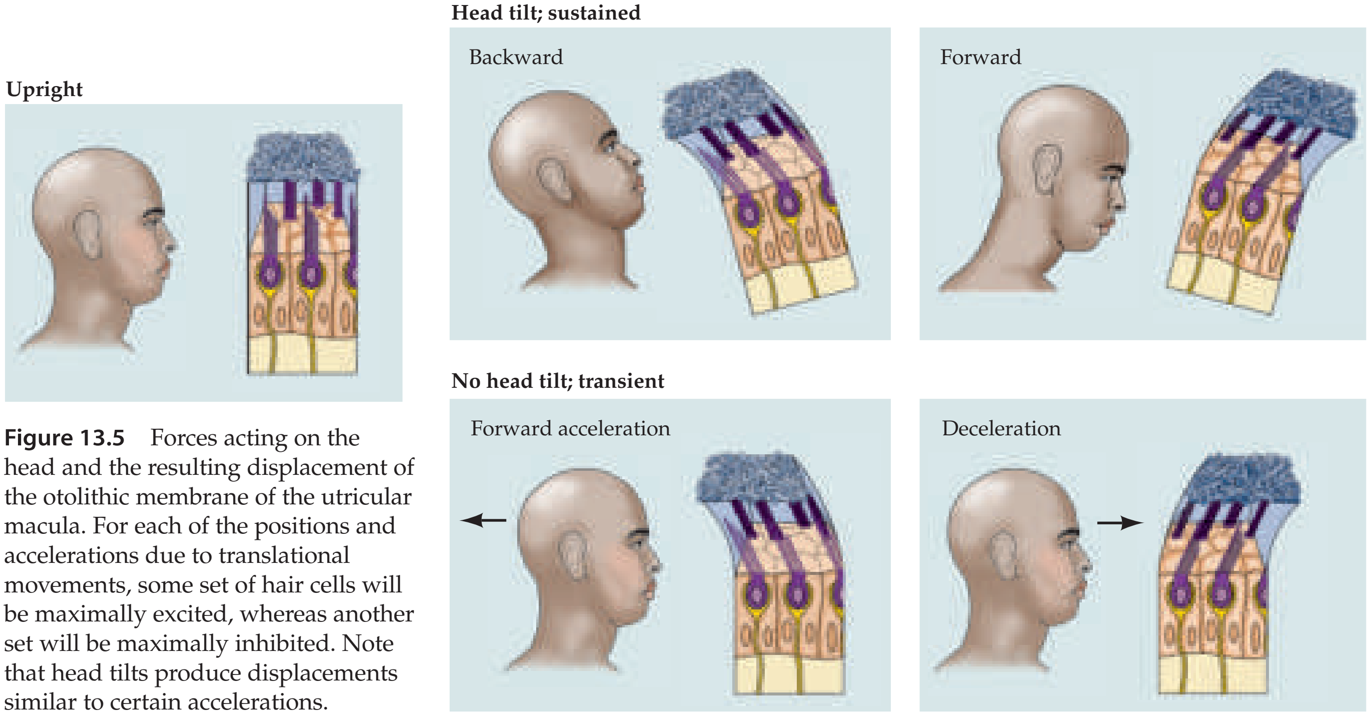


Figure 13.5 Forces acting on the head and the resulting displacement of the otolithic membrane of the utricular macula. For each of the positions and accelerations due to translational movements, some set of hair cells will be maximally excited, whereas another set will be maximally inhibited. Note that head tilts produce displacements similar to certain accelerations.

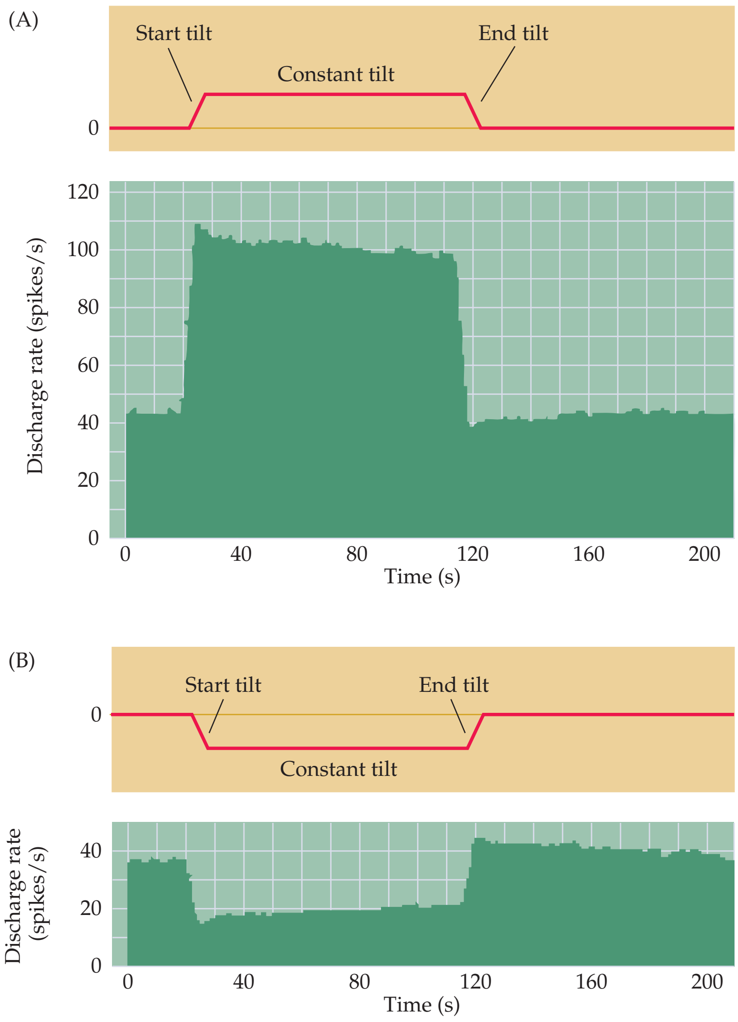


Figure 13.6 Response of a vestibular nerve axon from an otolith organ (the utricle in this example). (A) The stimulus (top) is a change in head tilt. The spike histogram shows the neuron's response to tilting in a particular direction. (B) A response of the same fiber to tilting in the opposite direction. (After Goldberg and Fernandez, 1976.)

steady and relatively high firing rate when the head is upright. The change in firing rate in response to a given movement can be either sustained or transient, thereby signaling either absolute head position or linear acceleration. An example of the sustained response of a vestibular nerve fiber innervating the utricle is shown in Figure 13.6. The responses were recorded from axons in a monkey seated in a chair that could be tilted for several seconds to produce a steady force. Prior to the tilt, the axon has a high firing rate, which increases or decreases depending on the direction of the tilt. Notice also that the response remains at a high level as long as the tilting force remains constant; thus, such neurons faithfully encode the static force being applied to the head (Figure 13.6A). When the head is returned to the original position, the firing level of the neurons returns to baseline value. Conversely, when the tilt is in the opposite direction, the neurons respond by decreasing their firing rate below the resting level (Figure 13.6B) and remain depressed as long as the static force continues. In a similar fashion, transient increases or decreases in firing rate from spontaneous levels signal the direction of linear accelerations of the head.

The range of orientations of hair bundles within the otolith organs enables them to transmit information about linear forces in every direction the body moves (see Figure 13.4C). The utricle, which is primarily concerned with motion in the horizontal plane, and the saccule, which is concerned with vertical motion, combine to effectively gauge the linear forces acting on the head at any instant in three dimensions. Tilts of the head off the horizontal plane and translational movements of the head in any direction stimulate a distinct subset of hair cells in the saccular and utricular maculae, while simultaneously suppressing the responses of other hair cells in these organs. Ultimately, variations in hair cell polarity within the otolith organs produce patterns of vestibular nerve fiber activity that, at a population level, can unambiguously encode head position and the forces that influence it.

The Semicircular Canals

Whereas the otolith organs are primarily concerned with head translations and orientation with respect to gravity, the semicircular canals sense head *rotations,* arising either from self-induced movements or from angular accelerations of the head imparted by external forces. Each of the three semicircular canals has at its base a bulbous expansion called the **ampulla** (Figure 13.7), which houses the sensory epithelium, or **crista**, that contains the hair cells. The structure of the canals suggests how they detect the angular accelerations that arise through rotation of the head. The hair bundles extend out of the crista into a gelatinous mass, the **cupula**, that bridges the width of the ampulla, forming a fluid barrier through which endolymph cannot circulate. As a result, the relatively compliant cupula is distorted by movements of the endolymphatic fluid. When the head turns in the plane of one of the semicircular canals, the inertia of the endolymph produces a force across the cupula, distending it away from the direction of head movement and causing a displacement of the hair bundles within the crista (Figure 13.8A,B). In contrast, linear accelerations of the head produce equal forces on the two sides of the cupula, so the hair bundles are not displaced.

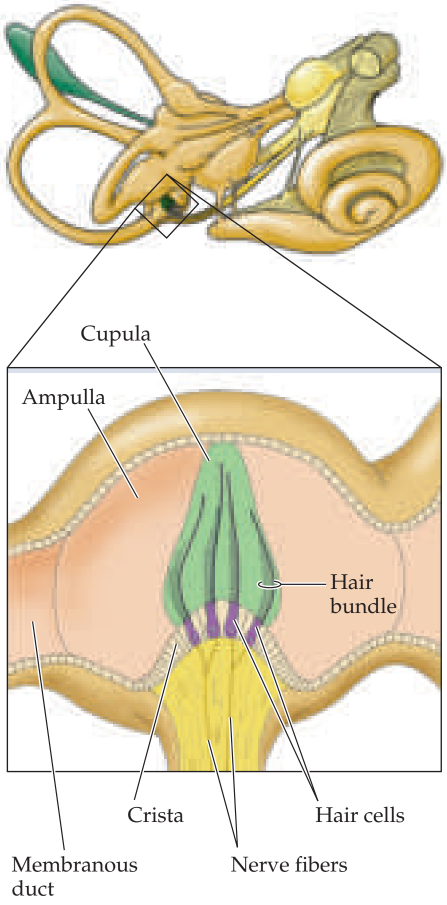


Figure 13.7 The ampulla of the posterior semicircular canal showing the crista, hair bundles, and cupula. The cupula is distorted by the fluid in the membranous canal when the head rotates.

Unlike the saccular and utricular maculae, all of the hair cells in the crista within each semicircular canal are organized with their kinocilia pointing in the same direction (see Figure 13.2C). Thus, when the cupula moves in the appropriate direction, the entire population of hair cells is depolarized and activity in all of the innervating axons increases. When the cupula moves in the opposite direction, the population is hyperpolarized and neuronal activity decreases. Deflections orthogonal to the excitatory–inhibitory direction produce little or no response.

Each semicircular canal works in concert with the partner located on the other side of the head that has its hair cells aligned oppositely. There are three such pairs: the two pairs of horizontal canals, and the superior canal on each side working with the posterior canal on the other side (Figure 13.8C). Head rotation deforms the cupula in opposing directions for the two partners, resulting in opposite changes in their firing rates (Box C). Thus, the orientation of the horizontal canals makes them selectively sensitive to rotation in the horizontal plane. More specifically, the hair cells in the canal towards which the head is turning are depolarized, while those on the other side are hyperpolarized.

For example, when the head accelerates to the left, the cupula is pushed toward the kinocilium in the left horizontal canal, and the firing rate of the relevant axons in the left vestibular nerve increases. In contrast, the cupula in the right horizontal canal is pushed away from the kinocilium, with a concomitant decrease in the firing rate of the related neurons. If the head movement is

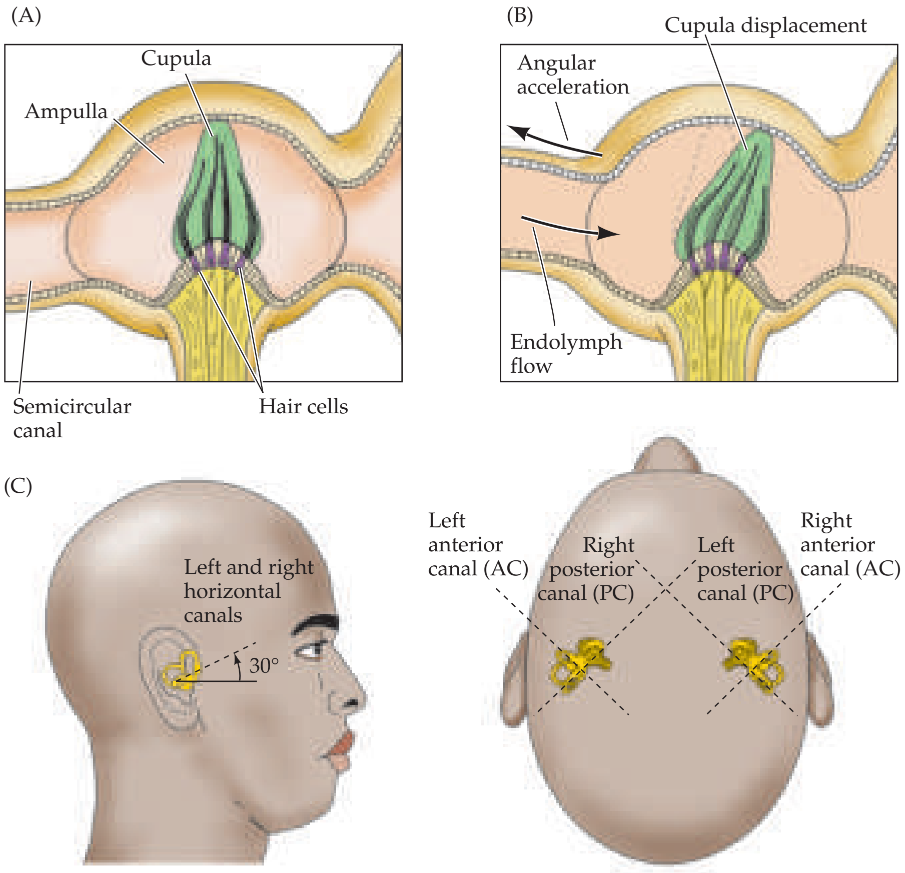

(A)
Cupula
Ampulla
Semicircular canal
Hair cells
(B)
Cupula displacement
Angular acceleration
Endolymph flow
(C)
Left and right horizontal canals
30°
Left anterior canal (AC)
Right posterior canal (PC)
Left posterior canal (PC)
Right anterior canal (AC)

Figure 13.8 Functional organization of the semicircular canals. (A) The position of the cupula without angular acceleration. (B) Distortion of the cupula during angular acceleration. When the head is rotated in the plane of the canal (arrow outside canal), the inertia of the endolymph creates a force (arrow inside the canal) that displaces the cupula. (C) Arrangement of the canals in pairs. The two horizontal canals form a pair; the right anterior canal (AC) and the left posterior canal (PC) form a pair; and the left AC and the right PC form a pair.

to the right, the result is just the opposite. This push–pull arrangement operates for all three pairs of canals; the pair whose activity is modulated is in the plane of the rotation, and the member of the pair whose activity is increased is on the side toward which the head is turning. The net result is a system that provides information about the rotation of the head in any direction.

How Semicircular Canal Neurons Sense Angular Accelerations

Like axons that innervate the otolith organs, the vestibular fibers that innervate the semicircular canals exhibit a high level of spontaneous activity. As a result, they can transmit information by either increasing or decreasing their firing rate, thus more effectively encoding head movements (see above). The bidirectional responses of fibers innervating the hair cells of the semicircular canal have been studied by recording the axonal firing rates in a monkey’s

Box C

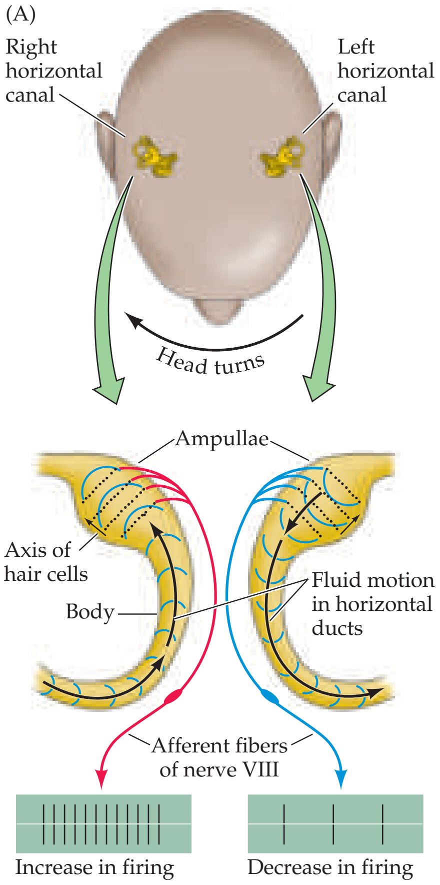
Throwing Cold Water on the Vestibular System

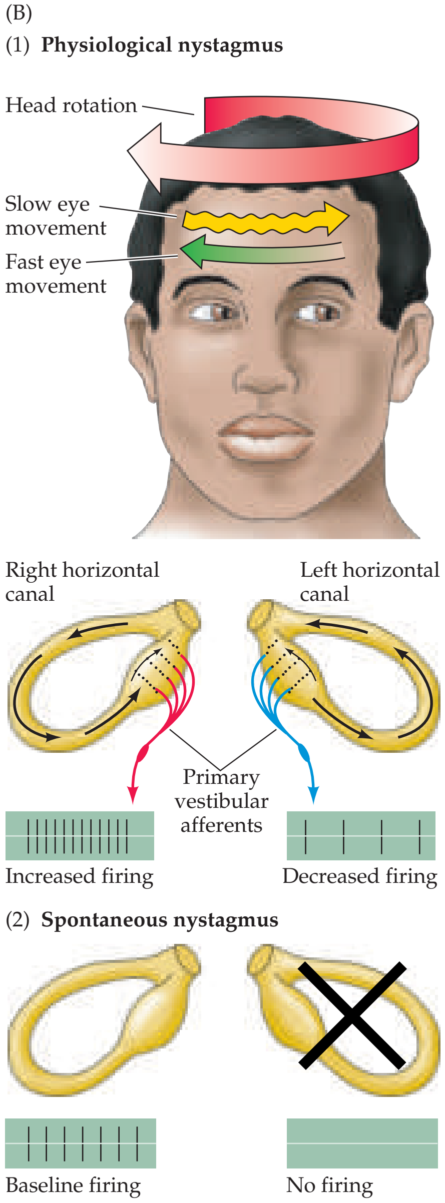
Testing the integrity of the vestibular system can indicate much about the condition of the brainstem, particularly in comatose patients.

Normally, when the head is not being rotated, the output of the nerves from the right and left sides are equal; thus, no eye movements occur. When the head is rotated in the horizontal plane, the vestibular afferent fibers on the side toward the turning motion increase their firing rate, while the afferents on the opposite side decrease their firing rate (Figures A and B). The net difference in firing rates then leads to slow movements of the eyes counter to the turning motion. This reflex response generates the slow component of a normal eye movement pattern called physiological nystagmus, which means "nodding" or oscillatory movements of the eyes (Figure B1). (The fast component is a saccade that resets the eye position; see Chapter 19.)

Pathological nystagmus can occur if there is unilateral damage to the vestibular system. In this case, the silencing of the spontaneous output from the damaged side results in an unphysiological difference in firing rate because the spontaneous discharge from the intact side remains (Figure B2). The difference in firing rates causes nystagmus, even though no head movements are being made.

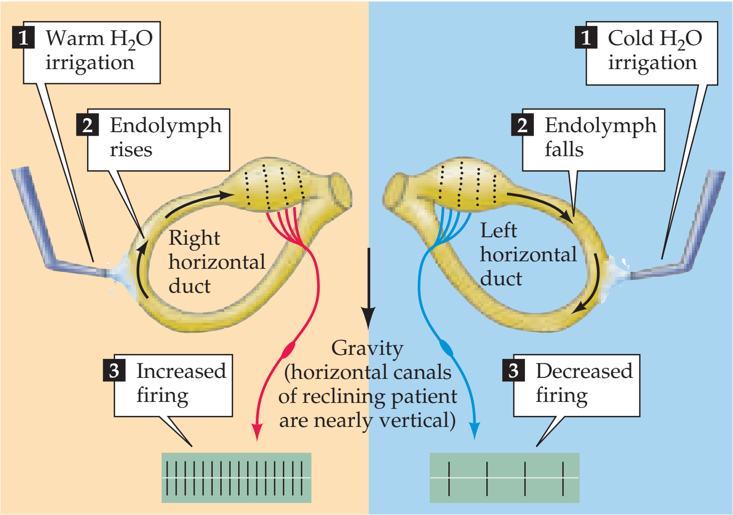
Responses to vestibular stimulation are thus useful in assessing the integrity of the brainstem in unconscious patients. If the individual is placed on his or her back and the head is elevated to about 30° above horizontal, the horizontal semicircular canals lie in an almost vertical orientation. Irrigating one ear with cold water will then lead to spontaneous eye movements because convection currents in the canal mimic rotatory head movements away from the irrigated ear (Figure C). In normal individuals, these eye movements consist of a slow movement toward the irrigated ear and a fast movement away from it. The fast movement is most readily detected by the observer, and the significance of its direction can be kept in mind by using the


(A)
Right horizontal canal
Left horizontal canal
Head turns
Ampullae
Axis of hair cells
Body
Fluid motion in horizontal ducts
Afferent fibers of nerve VIII
Increase in firing
Decrease in firing


(B)
(1) Physiological nystagmus
Head rotation
Slow eye movement
Fast eye movement
Right horizontal canal
Left horizontal canal
Primary vestibular afferents
Increased firing
Decreased firing
(2) Spontaneous nystagmus
Baseline firing
No firing

(A) View looking down on the top of a person's head illustrates the fluid motion generated in the left and right horizontal canals, and the changes in vestibular nerve firing rates when the head turns to the right. (B) In normal individuals, rotating the head elicits physiological nystagmus (1), which consists of a slow eye movement counter to the direction of head turning. The slow component of the eye movements is due to the net differences in left and right vestibular nerve firing rates acting via the central circuit diagrammed in Figure 13.10. Spontaneous nystagmus (2), where the eyes move rhythmically from side to side in the absence of any head movements, occurs when one of the canals is damaged. In this situation, net differences in vestibular nerve firing rates exist even when the head is stationary because the vestibular nerve innervating the intact canal fires steadily when at rest, in contrast to a lack of activity on the damaged side.

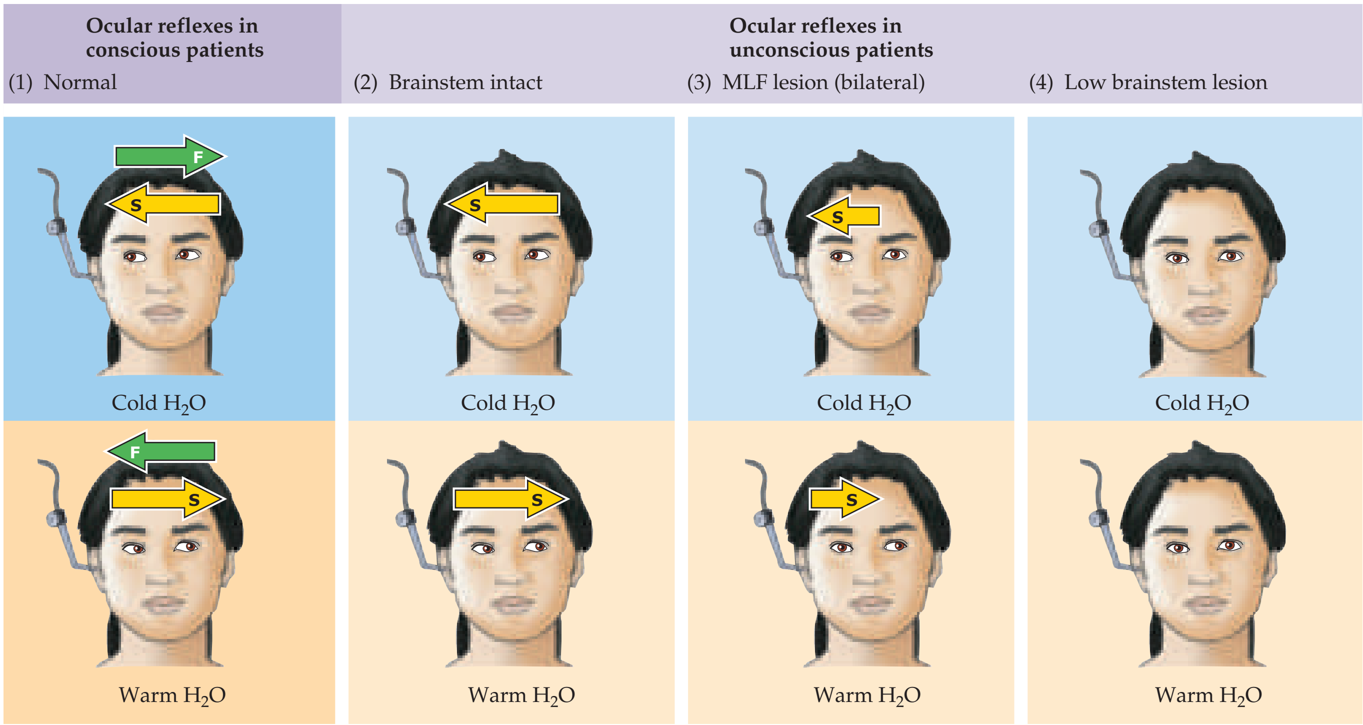
(C)


1 Warm H_2O irrigation
2 Endolymph rises
Right horizontal duct
3 Increased firing
Gravity (horizontal canals of reclining patient are nearly vertical)
1 Cold H_2O irrigation
2 Endolymph falls
Left horizontal duct
3 Decreased firing

(C) Caloric testing of vestibular function is possible because irrigating an ear with water slightly warmer than body temperature generates convection currents in the canal that mimic the endolymph movement induced by turning the head to the irrigated side. Irrigation with cold water induces the opposite effect. These currents result in changes in the firing rate of the associated vestibular nerve, with an increased rate on the warmed side and a decreased rate on the chilled side. As in head rotation and spontaneous nystagmus, net differences in firing rates generate eye movements.

mnemonic COWS ("Cold Opposite, Warm Same"). This same test can also be used in unconscious patients. In patients who are comatose due to dysfunction of both cerebral hemispheres but whose brainstem is intact, saccadic movements are no longer made and the response to cold water consists of only the slow movement component of the eyes to side of the irrigated ear (Figure D). In the presence of brainstem lesions involving either the vestibular nuclei themselves, the connections from the vestibular nuclei to oculomotor nuclei (the third, fourth, or sixth cranial nerves), or the peripheral nerves exiting these nuclei, vestibular responses are abolished (or altered, depending on the severity of the lesion).

(D)


Ocular reflexes in conscious patients
(1) Normal
Ocular reflexes in unconscious patients
(2) Brainstem intact
(3) MLF lesion (bilateral)
(4) Low brainstem lesion
F
S
Cold H_2O
Warm H_2O

(D) Caloric testing can be used to test the function of the brainstem in an unconscious patient. The figures show eye movements resulting from cold or warm water irrigation in one ear for (1) a normal subject, and in three different conditions in an unconscious patient: (2) with the brainstem intact; (3) with a lesion of the medial longitudinal fasciculus (MLF; note that irrigation in this case results in lateral movement of the eye only on the less active side); and (4) with a low brainstem lesion (see Figure 13.10).

vestibular nerve. Seated in a chair, the monkey was rotated continuously in one direction during three phases: an initial period of acceleration, then a periord of several seconds at constant velocity, and finally a period of sudden deceleration to a stop (Figure 13.9). The maximum firing rates observed correspond to the period of acceleration; the maximum inhibition corresponds to the period of deceleration. During the constant-velocity phase, the response adapts so that the firing rate subsides to resting level; after the movement stops, the neuronal activity decreases transiently before returning to the resting level.

Neurons innervating paired semicircular canals have a complementary response pattern. Note that the rate of adaptation (on the order of tens of seconds) corresponds to the time it takes the cupula to return to its undistorted state (and for the hair bundles to return to their undeflected position); adaptation therefore can occur while the head is still turning, as long as a constant angular velocity is maintained. Such constant forces are rare in nature, although they are encountered on ships, airplanes, and space vehicles, where prolonged acceleratory arcs are sometimes described.

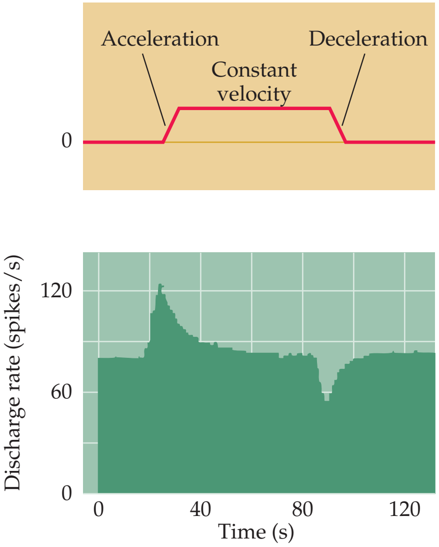


Figure 13.9 Response of a vestibular nerve axon from the semicircular canal to angular acceleration. The stimulus (top) is a rotation that first accelerates, then maintains constant velocity, and then decelerates the head. The axon increases its firing above resting level in response to the acceleration, returns to resting level during constant velocity, then decreases its firing rate below resting level during deceleration; these changes in firing rate reflect inertial effects on the displacement of the cupula. (After Goldberg and Fernandez, 1971.)

Central Pathways for Stabilizing Gaze, Head, and Posture

The vestibular end organs communicate via the vestibular branch of cranial nerve VIII with targets in the brainstem and the cerebellum that process much of the information necessary to compute head position and motion. As with the cochlear nerve, the vestibular nerves arise from a population of bipolar neurons, the cell bodies of which in this instance reside in the **vestibular nerve ganglion** (also called **Scarpa's ganglion**; see Figure 13.1). The distal processes of these cells innervate the semicircular canals and the otolith organs, while the central processes project via the vestibular portion of cranial nerve VIII to the **vestibular nuclei** (and also directly to the cerebellum; Figure 13.10). The vestibular nuclei are important centers of integration, receiving input from the vestibular nuclei of the opposite side, as well as from the cerebellum and the visual and somatic sensory systems. Because vestibular and auditory fibers run together in the eighth nerve, damage to this structure often results in both auditory and vestibular disturbances.

The central projections of the vestibular system participate in three major classes of reflexes: (1) helping to maintain equilibrium and gaze during movement, (2) maintaining posture, and (3) maintaining muscle tone. The first of these reflexes helps coordinate head and eye movements to keep gaze fixated on objects of interest during movements (other functions include protective or escape reactions; see Box D). The **vestibulo-ocular reflex** (**VOR**) in particular is a mechanism for producing eye movements that counter head movements, thus permitting the gaze to remain fixed on a particular point (Box C; see also Chapter 19). For example, activity in the left horizontal canal induced by leftward rotary acceleration of the head excites neurons in the left vestibular nucleus and results in compensatory eye movements to the right. This effect is due to excitatory projections from the vestibular nucleus to the contralateral nucleus abducens that, along with the oculomotor nucleus, help execute conjugate eye movements.

For instance, horizontal movement of the two eyes toward the right requires contraction of the left medial and right lateral rectus muscles. Vestibular nerve fibers originating in the left horizontal semicircular canal project to the medial and lateral vestibular nuclei (see Figure 13.10). Excitatory fibers from the medial vestibular nucleus cross to the contralateral abducens nucleus, which has two outputs. One of these is a motor pathway

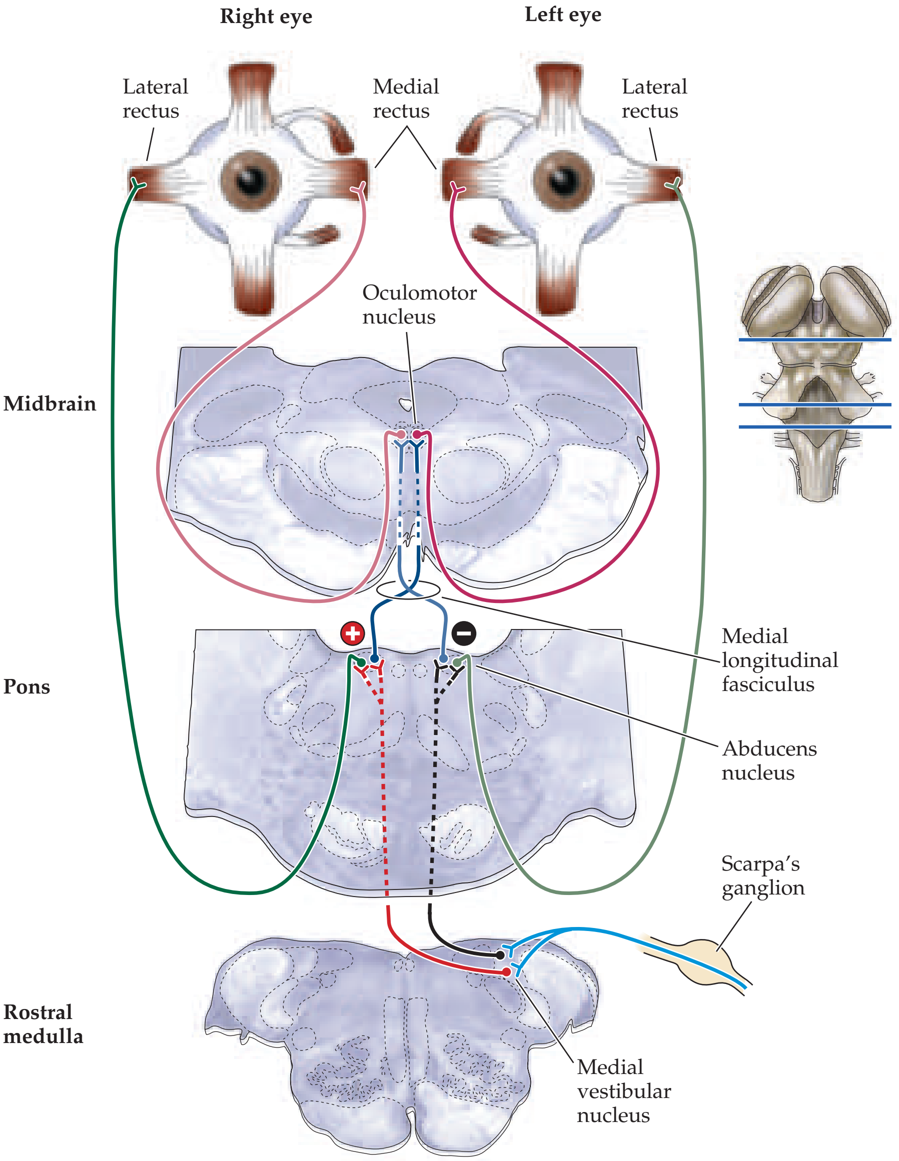

Right eye
Left eye
Lateral rectus
Medial rectus
Lateral rectus
Oculomotor nucleus
Midbrain
Pons
Rostral medulla
Medial longitudinal fasciculus
Abducens nucleus
Scarpa's ganglion
Medial vestibular nucleus

Figure 13.10 Connections underlying the vestibulo-ocular reflex. Projections of the vestibular nucleus to the nuclei of cranial nerves III (oculomotor) and VI (abducens). The connections to the oculomotor nucleus and to the contralateral abducens nucleus are excitatory (red), whereas the connections to ipsilateral abducens nucleus are inhibitory (black). There are connections from the oculomotor nucleus to the medial rectus of the left eye and from the adbucens nucleus to the lateral rectus of the right eye. This circuit moves the eyes to the right, that is, in the direction away from the left horizontal canal, when the head rotates to the left. Turning to the right, which causes increased activity in the right horizontal canal, has the opposite effect on eye movements. The projections from the right vestibular nucleus are omitted for clarity.

that causes the lateral rectus of the right eye to contract; the other is an excitatory projection that crosses the midline and ascends via the **medial longitudinal fasciculus** to the left oculomotor nucleus, where it activates neurons that cause the medial rectus of the left eye to contract. Finally, inhibitory neurons project from the medial vestibular nucleus to the left abducens nucleus, directly causing the motor drive on the lateral rectus of the left eye to decrease and also indirectly causing the right medial rectus to relax. The consequence of these several connections is that excitatory input from the horizontal canal on one side produces eye movements toward the opposite side. Therefore, turning the head to the left causes eye movements to the right.

In a similar fashion, head turns in other planes activate other semicircular canals, causing other appropriate compensatory eye movements. Thus, the VOR also plays an important role in vertical gaze stabilization in response to the linear vertical head oscillations that accompany locomotion, and in response to vertical angular accelerations of the head, as can occur when riding on a swing. The rostrocaudal set of cranial nerve nuclei involved in the VOR (i.e., the vestibular, abducens, and oculomotor nuclei), as well as the VOR's persistence in the unconscious state, make this reflex especially useful for detecting brainstem damage in the comatose patient (see Box C).

Loss of the VOR can have severe consequences. A patient with vestibular damage finds it difficult or impossible to fixate on visual targets while the head is moving, a condition called **oscillopsia** ("bouncing vision"). If the damage is unilateral, the patient usually recovers the ability to fixate objects during head movements. However, a patient with bilateral loss of vestibular function has the persistent and disturbing sense that the world is moving when the head moves. The underlying problem in such cases is that information about head and body movements normally generated by the vestibular organs is not available to the oculomotor centers, so that compensatory eye movements cannot be made.

Descending projections from the vestibular nuclei are essential for postural adjustments of the head, mediated by the vestibulo-cervical reflex (VCR), and body, mediated by the vestibulo-spinal reflex (VSR). As with the VOR, these postural reflexes are extremely fast, in part due to the small number of synapses interposed between the vestibular organ and the relevant motor neurons (Box D). Like the VOR, the VCR and the VSR are both compromised in patients with bilateral vestibular damage. Such patients exhibit diminished head and postural stability, resulting in gait deviations; they also have difficulty balancing. These balance defects become more pronounced in low light or while walking on uneven surfaces, indicating that balance normally is the product of vestibular, visual, and proprioceptive inputs.

The anatomical substrate for the VCR involves the medial vestibular nucleus, axons from which descend in the medial longitudinal fasciculus to reach the upper cervical levels of the spinal cord (Figure 13.11). This pathway regulates head position by reflex activity of neck muscles in response to stimulation of the semicircular canals from rotational accelerations of the head. For example, during a downward pitch of the body (e.g., tripping), the superior canals are activated and the head muscles reflexively pull the head up. The dorsal flexion of the head initiates other reflexes, such as forelimb extension and hindlimb flexion, to stabilize the body and protect against a fall (see Chapter 16).

The VSR is mediated by a combination of pathways, including the lateral and medial vestibulospinal tracts and the reticulospinal tract. The inputs from the otolith organs project mainly to the lateral vestibular nucleus, which in turn sends axons in the lateral vestibulospinal tract to the spinal cord (see Figure 13.11). These axons terminate monosynaptically on extensor motor neurons, and they disynaptically inhibit flexor motor neurons; the net result is a powerful excitatory influence on the extensor (antigravity) muscles. When hair cells in the otolith organs are activated, signals reach the medial part of the ventral horn. By activating the ipsilateral pool of motor neurons innervating extensor muscles in the trunk and limbs, this pathway mediates balance and the maintenance of upright posture.

Decerebrate rigidity, characterized by rigid extension of the limbs, arises when the brainstem is transected above the level of the vestibular nucleus. Decerebrate rigidity in experimental animals is relieved when the vestibular nuclei are lesioned, underscoring the importance of the vestibular system to the maintenance of muscle tone. The tonic activation of extensor muscles in

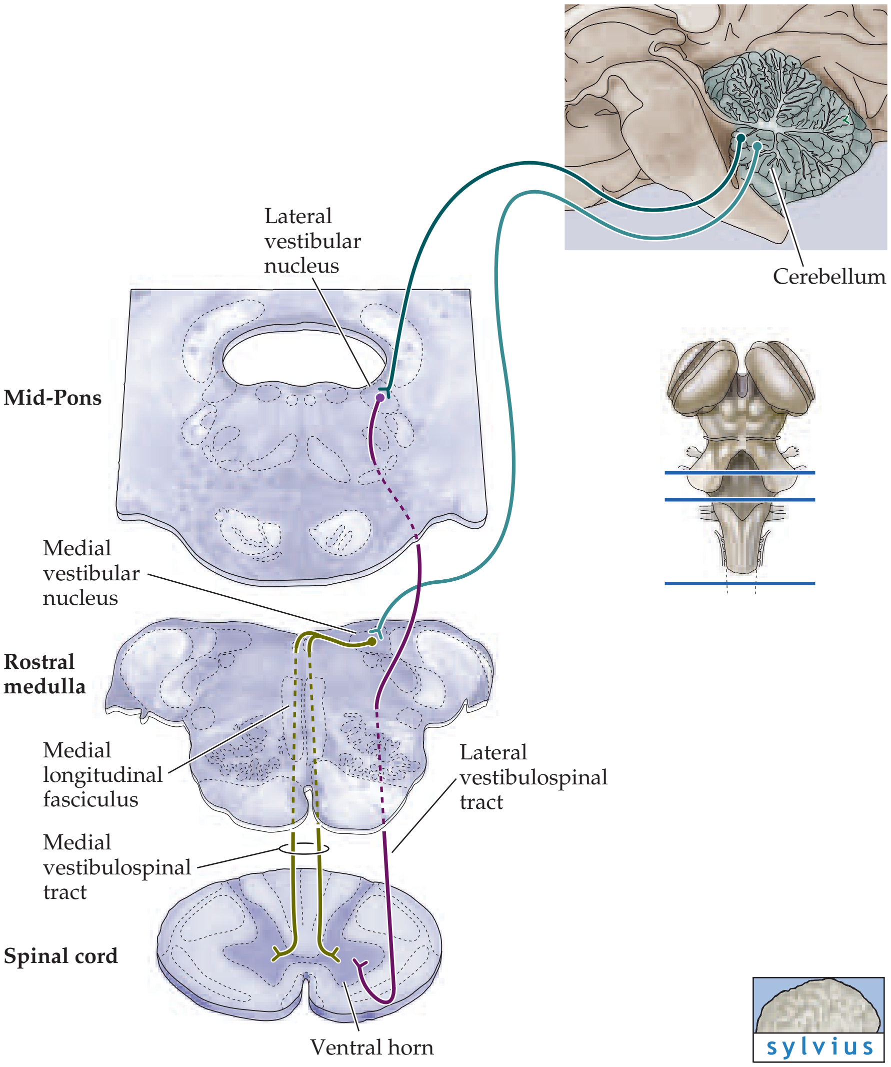

Lateral vestibular nucleus
Cerebellum
Mid-Pons
Medial vestibular nucleus
Rostral medulla
Medial longitudinal fasciculus
Lateral vestibulospinal tract
Medial vestibulospinal tract
Spinal cord
Ventral horn

Figure 13.11 Descending projections from the medial and lateral vestibular nuclei to the spinal cord underlie the VCR and VSR. The medial vestibular nuclei project bilaterally in the medial longitudinal fasciculus to reach the medial part of the ventral horns and mediate head reflexes in response to activation of semicircular canals. The lateral vestibular nucleus sends axons via the lateral vestibular tract to contact anterior horn cells innervating the axial and proximal limb muscles. Neurons in the lateral vestibular nucleus receive input from the cerebellum, allowing the cerebellum to influence posture and equilibrium.

decerebrate rigidity suggests further that the vestibulospinal pathway is normally suppressed by descending projections from higher levels of the brain, especially the cerebral cortex (see also Chapter 16).

Vestibular Pathways to the Thalamus and Cortex

In addition to these several descending projections, the superior and lateral vestibular nuclei send axons to the ventral posterior nuclear complex of the thalamus, which in turn projects to two cortical areas relevant to vestibular

Box D

Mauthner Cells in Fish

A primary function of the vestibular system is to provide information about the direction and speed of ongoing movements, ultimately enabling rapid, coordinated reflexes to compensate for both self-induced and externally generated forces. One of the most impressive and speediest vestibular-mediated reflexes is the tail-flip escape behavior of fish (and larval amphibians), a stereotyped response that allows a potential prey to elude its predators (Figure A; tap on the side of a fish tank if you want to observe the reflex). In response to a perceived risk, fish flick their tail and are thus propelled laterally away from the approaching threat.

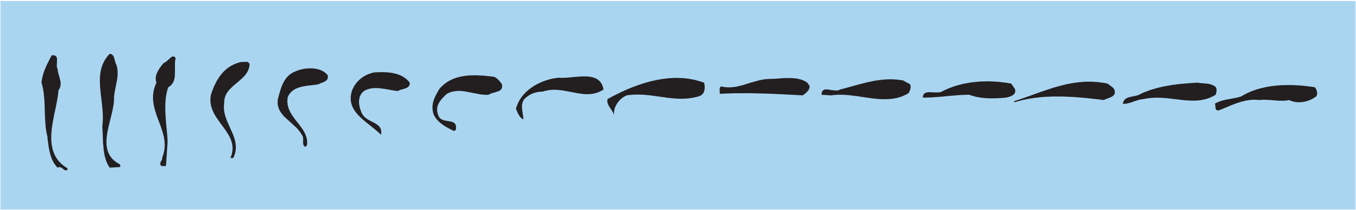
The circuitry underlying the tail-flip escape reflex includes a pair of giant medullary neurons called Mauthner cells, their vestibular inputs, and the spinal cord motor neurons to which the Mauthner cells project. (In most fish, there is one pair of Mauthner cells in a stereotypic location. Thus, these cells can be consistently visualized and studied from animal to animal.) Movements in the water, such as might be caused by an approaching predator, excite saccular hair cells in the vestibular labyrinth. These receptor potentials are transmitted via the central processes of vestibular ganglion cells in cranial nerve VIII to the two Mauthner cells in the brainstem. As in the vestibulo-spinal pathway in humans, the Mauthner cells project directly to spinal motor neurons. The small number of synapses intervening between the receptor cells and the motor neurons is one of the ways that this circuit has been optimized for speed by natural selection, an arrangement evident in humans as well. The large size of the Mauthner axons is another; the axons from these cells in a goldfish are about 50 μm in diameter.

The optimization for speed and direction in the escape reflex also is reflected in the synapses vestibular nerve afferents make on each Mauthner cell (Figure B). These connections are electrical synapses that allow rapid and faithful transmission of the vestibular signal.

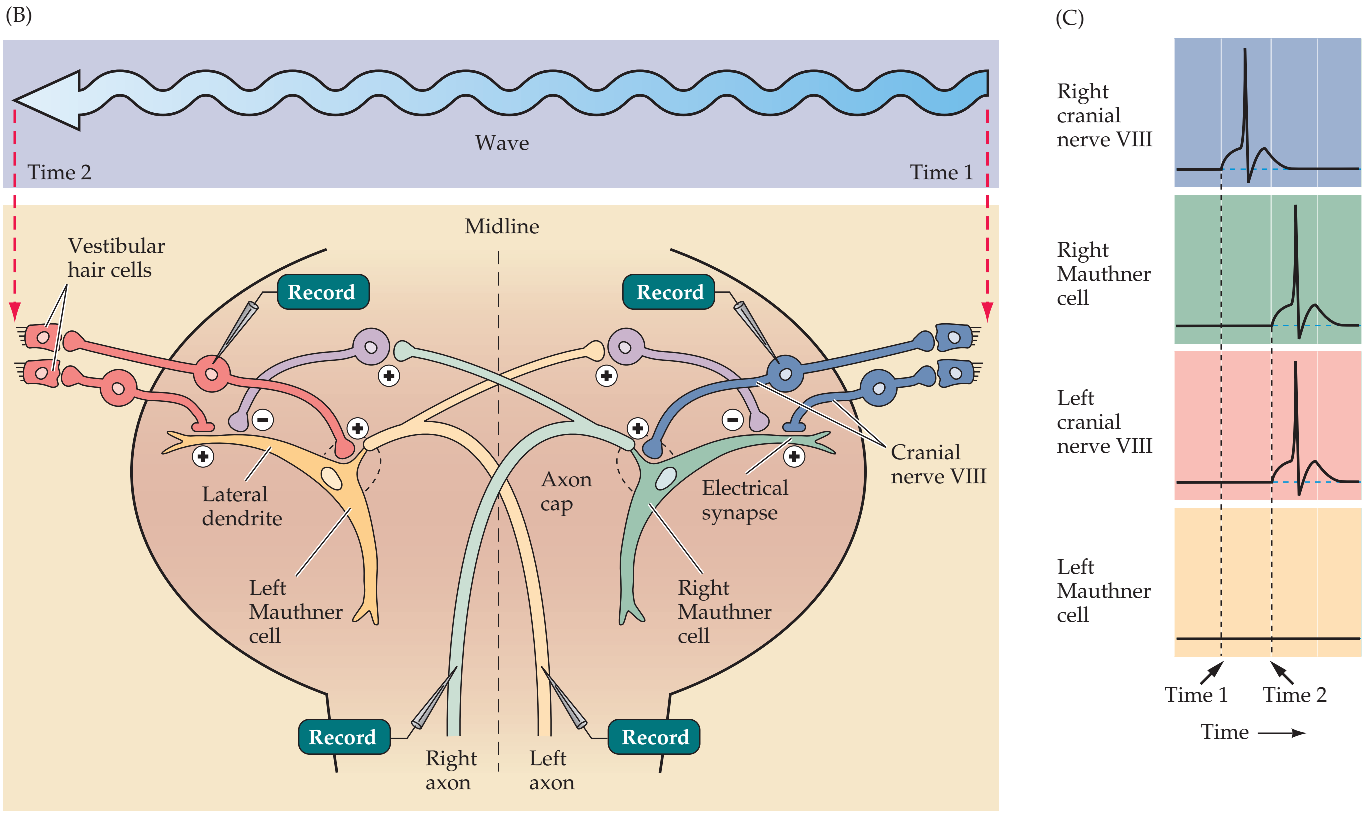
An appropriate direction for escape is promoted by two features: (1) each Mauthner cell projects only to contralateral motor neurons; and (2) a local network of bilaterally projecting interneurons inhibits activity in the Mauthner cell away from the side on which the vestibular activity originates. In this way, the Mauthner cell on one side faithfully generates action potentials that command contractions of contralateral tail musculature, thus moving the fish out of the path of the oncoming predator. Conversely, the Mauthner cell on the opposite side is silenced by the local inhibitory network during the response (Figure C).

(A) Bird's-eye view of the sequential body orientations of a fish engaging in a tail-flip escape behavior, with time progressing from left to right. This behavior is largely mediated by vestibular inputs to Mauthner cells.

(A)



sensations (Figure 13.12). One of these cortical targets is just posterior to the primary somatosensory cortex, near the representation of the face; the other is at the transition between the somatic sensory cortex and the motor cortex (Brodmann's area 3a; see Chapter 8). Electrophysiological studies of individual neurons in these areas show that the relevant cells respond to proprioceptive and visual stimuli as well as to vestibular stimuli. Many of these neurons are activated by moving visual stimuli as well as by rotation of the body (even with the eyes closed), suggesting that these cortical regions are involved in the perception of body orientation in extrapersonal space. Con-


(B)
Wave
Time 2
Time 1
Midline
Vestibular hair cells
Record
Record
Lateral dendrite
Left Mauthner cell
Axon cap
Electrical synapse
Right Mauthner cell
Cranial nerve VIII
Record
Record
Right axon
Left axon
(C)
Right cranial nerve VIII
Right Mauthner cell
Left cranial nerve VIII
Left Mauthner cell
Time 1
Time 2
Time →

(B) Diagram of synaptic events in the Mauthner cells of a fish in response to a disturbance in the water coming from the right. (C) Complementary responses of the right and left Mauthner cells mediating the escape response. Times 1 and 2 correspond to those indicated in Figure B. (After Furshpan and Furukuwa, 1962.)

The Mauthner cells in fish are analogous to the reticulospinal and vestibulospinal pathways that control balance, posture, and orienting movements in mammals. The equivalent behavioral responses in humans are evident in a friendly game of tag, or more serious endeavors.

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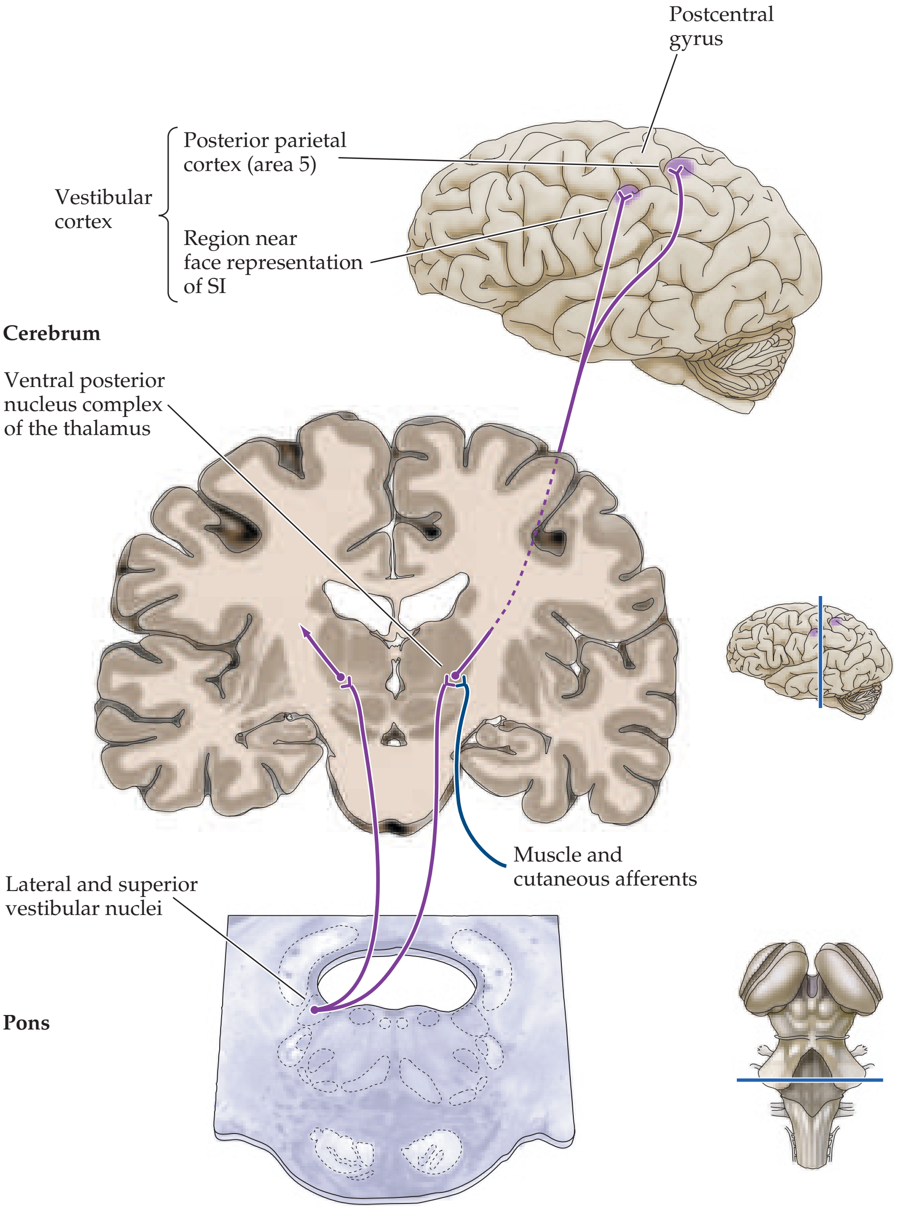
sistent with this interpretation, patients with lesions of the right parietal cortex suffer altered perception of personal and extra-personal space, as discussed in greater detail in Chapter 25.

Summary

The vestibular system provides information about the motion and position of the body in space. The sensory receptor cells of the vestibular system are located in the otolith organs and the semicircular canals of the inner ear. The

Figure 13.12 Thalamocortical pathways carrying vestibular information. The lateral and superior vestibular nuclei project to the thalamus. From the thalamus, the vestibular neurons project to the vicinity of the central sulcus near the face representation. Sensory inputs from the muscles and skin also converge on thalamic neurons receiving vestibular input (see Chapter 9).

sylvius


Postcentral gyrus
Posterior parietal cortex (area 5)
Vestibular cortex
Region near face representation of SI
Cerebrum
Ventral posterior nucleus complex of the thalamus
Muscle and cutaneous afferents
Lateral and superior vestibular nuclei
Pons

otolith organs provide information necessary for postural adjustments of the somatic musculature, particularly the axial musculature, when the head tilts in various directions or undergoes linear accelerations. This information represents linear forces acting on the head that arise through static effects of gravity or from translational movements. The semicircular canals, in contrast, provide information about rotational accelerations of the head. This latter information generates reflex movements that adjust the eyes, head, and body during motor activities. Among the best studied of these reflexes are eye movements that compensate for head movements, thereby stabilizing the visual scene when the head moves. Input from all the vestibular organs is integrated with input from the visual and somatic sensory systems to provide perceptions of body position and orientation in space.

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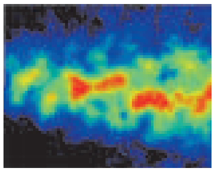
Chapter 14



The Chemical Senses

Overview

Three sensory systems associated with the nose and mouth—olfaction, taste, and the trigeminal or general chemosensory system—are dedicated to the detection of chemicals in the environment. The olfactory system detects airborne molecules called odorants. In humans, odors provide information about food, self, other people, animals, plants, and many other aspects of the environment. Olfactory information can influence feeding behavior, social interactions and, in many animals, reproduction. The taste (or gustatory) system detects ingested, primarily water-soluble molecules called tastants. Tastants provide information about the quality, quantity, and safety of ingested food. Finally, the trigeminal chemosensory system provides information about irritating or noxious molecules that come into contact with skin or mucous membranes of the eyes, nose, and mouth. All three of these chemosensory systems rely on receptors in the nasal cavity, mouth, or on the face that interact with the relevant molecules and generate receptor and action potentials, thus transmitting information about chemical stimuli to appropriate regions of the central nervous system.

The Organization of the Olfactory System

From an evolutionary perspective, the chemical senses—particularly olfaction—are deemed the “oldest” sensory systems; nevertheless, they remain in many ways the least understood of the sensory modalities. The olfactory system (Figure 14.1) is the most thoroughly studied component of the chemosensory triad and processes information about the identity, concentration, and quality of a wide range of chemical stimuli that we associate with our sense of smell. These stimuli, called **odorants**, interact with olfactory receptor neurons found in an epithelial sheet—the **olfactory epithelium**—that lines the interior of the nose (Figure 14.1A,B). The axons arising from the receptor cells project directly to neurons in the **olfactory bulb**, which in turn sends projections to the **pyriform cortex** in the temporal lobe as well as other structures in the forebrain (Figure 14.1C). The olfactory system is thus unique among the sensory systems in that it does not include a thalamic relay from primary receptors en route to a neocortical (six-layered) region that processes the sensory information. Instead, the pyriform cortex is three-layered **archicortex**—considered to be phlogenetically older than the neocortex—and thus represents a specialized processing center dedicated to olfaction. Projections from the pyriform cortex relay olfactory information via the thalamus to association areas of the neocortex (see Figure 14.1C, D). The olfactory tract also projects to a number of other targets in the forebrain, including the hypothalamus and amygdala. The further processing that

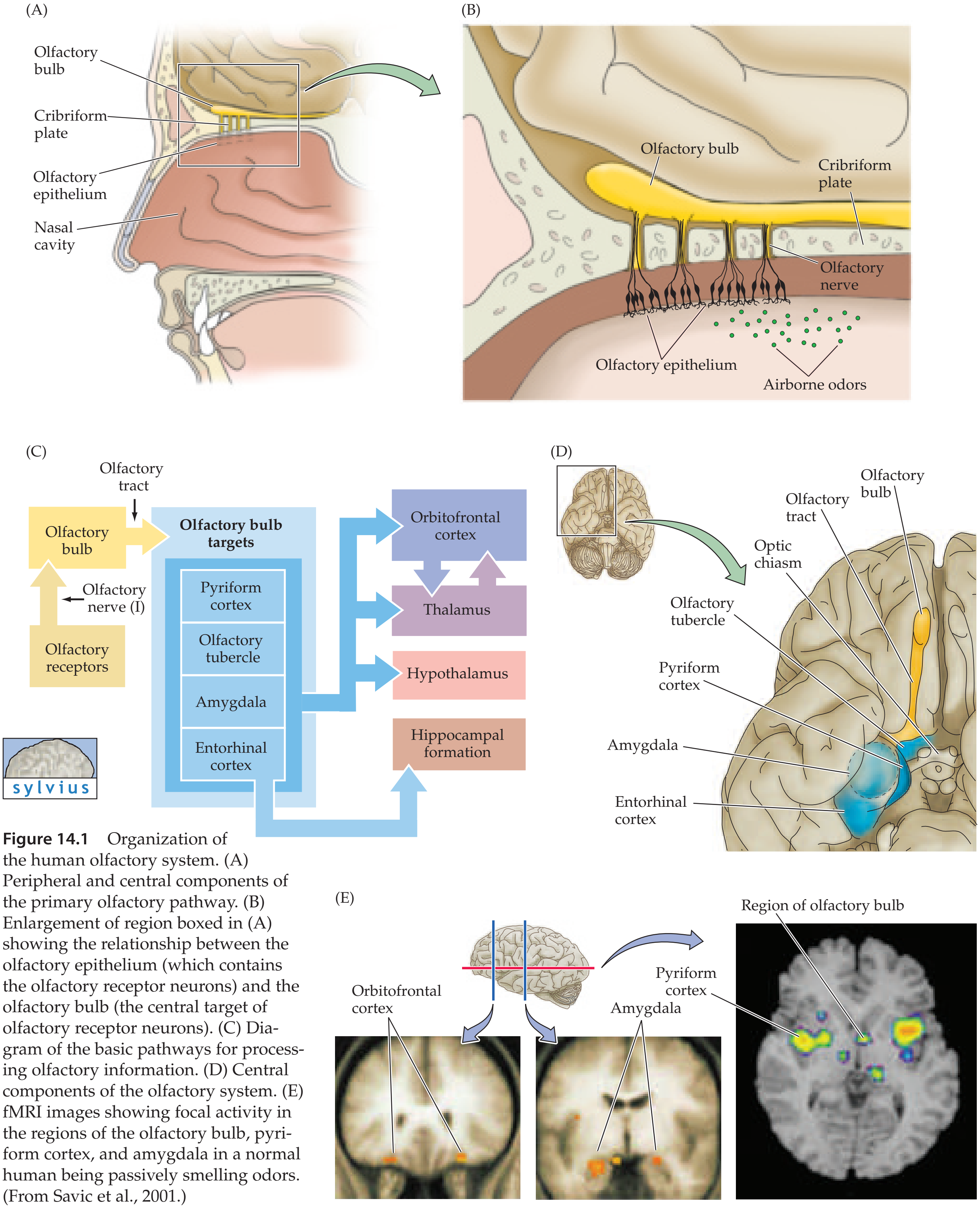

(A)
Olfactory bulb
Cribriform plate
Olfactory epithelium
Nasal cavity
(B)
Olfactory bulb
Cribriform plate
Olfactory nerve
Olfactory epithelium
Airborne odors
(C)
Olfactory tract
Olfactory bulb
Olfactory nerve (I)
Olfactory receptors
Olfactory bulb targets
Pyriform cortex
Olfactory tubercle
Amygdala
Entorhinal cortex
Orbitofrontal cortex
Thalamus
Hypothalamus
Hippocampal formation
(D)
Olfactory bulb
Olfactory tract
Optic chiasm
Olfactory tubercle
Pyriform cortex
Amygdala
Entorhinal cortex
(E)
Orbitofrontal cortex
Amygdala
Pyriform cortex
Region of olfactory bulb

Figure 14.1 Organization of the human olfactory system. (A) Peripheral and central components of the primary olfactory pathway. (B) Enlargement of region boxed in (A) showing the relationship between the olfactory epithelium (which contains the olfactory receptor neurons) and the olfactory bulb (the central target of olfactory receptor neurons). (C) Diagram of the basic pathways for processing olfactory information. (D) Central components of the olfactory system. (E) fMRI images showing focal activity in the regions of the olfactory bulb, pyriform cortex, and amygdala in a normal human being passively smelling odors. (From Savic et al., 2001.)

occurs in these various regions identifies the odorant and initiates appropriate motor, visceral, and emotional reactions to olfactory stimuli.

Despite its phylogenetic “age” and the unusual trajectory of olfactory information to the neocortex, the olfactory system abides by the basic principle that governs other sensory modalities: interactions with stimuli—in this case, airborne chemical odorants—at the periphery are transduced and encoded by receptors into electrical signals, which are then relayed to higher-order centers. Nevertheless, less is known about the central organization of the olfactory system than other sensory pathways. For example, the somatic sensory and visual cortices described in the preceding chapters all feature spatial maps of the relevant receptor surface, and the auditory cortex features frequency and other maps. Whether analogous maps of specific odorants (e.g., rose or pine) or odorant attributes (e.g., sweet or acrid) exist in the olfactory bulb or pyriform cortex is not yet known. Indeed, until recently it has been difficult to imagine what sensory qualities would be represented in an olfactory map, or what features might be processed in parallel as occurs in other sensory systems.

Olfactory Perception in Humans

In humans, olfaction is often considered the least acute of the senses, and a number of animals are obviously superior to humans in their olfactory abilities. This difference may reflect the larger number of olfactory receptor neurons (and odorant receptor molecules; see below) in the olfactory epithelium in many species and the proportionally larger area of the forebrain devoted to olfaction. In a 70-kg human, the surface area of the olfactory epithelium is approximately 10 cm^2. In contrast, a 3-kg cat has about 20 cm^2 of olfactory epithelium. Similarly, the relative size of the olfactory bulb and related structures versus the cortical hemispheres in a rodent or carnivore is quite large compared to that in humans. Humans are nonetheless quite good at detecting and identifying airborne molecules in the environment (Figure 14.2). For instance, the major aromatic constituent of bell pepper (2-isobutyl-3-methoxypyrazine) can be detected at a concentration of 0.01 n*M*. However, the threshold concentrations for detection and identification of other odorants vary greatly. Ethanol, for example, cannot be identified until its concentration reaches approximately 2 m*M*. Small changes in molecular structure can also lead to large perceptual differences: The molecule D-carvone smells like caraway seeds, whereas L-carvone smells like spearmint.

Since the number of odorants is very large, there have been several attempts to classify them in groups. The most widely used classification was developed in the 1950s by John Amoore, who divided odors into categories based on their perceived quality, molecular structure, and the fact that some people, called anosmics, have difficulty smelling one or another group. Amoore classified odorants as *pungent*, *floral*, *musky*, *earthy*, *ethereal*, *camphor*, *peppermint*, *ether*, and *putrid*; these categories are still used to describe odors, to study the cellular mechanisms of olfactory transduction, and to discuss the central representation of olfactory information. Nevertheless, this classification remains entirely empirical. A further complication in rationalizing the perception of odors is that their quality may change with concentration. For example, at low concentrations indole has a floral odor, whereas at higher concentrations it smells putrid. Despite these problems, the longevity of Amoore’s scheme makes clear that the olfactory system can identify odorant classes that have distinct perceptual qualities. Indeed, humans can per-

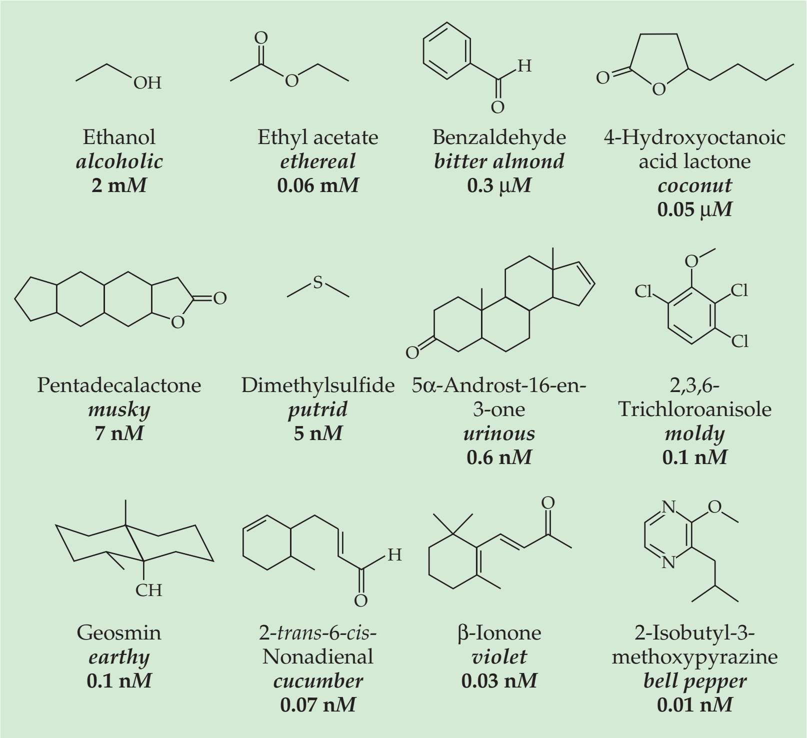

OH
O
O
H
O
O
O
Ethanol
alcoholic
2 mM
Ethyl acetate
ethereal
0.06 mM
Benzaldehyde
bitter almond
0.3 µM
4-Hydroxyoctanoic acid lactone
coconut
0.05 µM
O
O
S
O
O
Cl
Cl
Cl
Pentadecalactone
musky
7 nM
Dimethylsulfide
putrid
5 nM
5α-Androst-16-en-3-one
urinous
0.6 nM
2,3,6-Trichloroanisole
moldy
0.1 nM
CH
H
O
O
N
O
N
Geosmin
earthy
0.1 nM
2-*trans*-6-*cis*-Nonadienal
cucumber
0.07 nM
β-Ionone
violet
0.03 nM
2-Isobutyl-3-methoxypyrazine
bell pepper
0.01 nM

Figure 14.2 Chemical structure and human perceptual threshold for 12 common odorants. Molecules perceived at low concentrations are more lipid-soluble, whereas those with higher thresholds are more water-soluble. (After Pelosi, 1994.)

ceive distinct odorant molecules as a particular identifiable smell. Thus, coconuts, violets, cucumbers, and bell peppers all have a unique odor generated by a specific molecule. Most naturally occurring odors, however, are blends of several odorant molecules, even though they are typically experienced as a single smell (such as the perceptions elicited by perfumes or the bouquet of a wine).

Psychologists and neurologists have developed a variety of tests that measure the ability to detect common odors. Although most people are able to consistently identify a broad range of test odorants, others fail to identify one or more common smells (Figure 14.3). Such chemosensory deficits, called anosmias, are often restricted to a single odorant, suggesting that a specific element in the olfactory system, either an olfactory receptor gene (see below) or genes that control expression or function of a specific odorant receptor gene, is inactivated. Nevertheless, genetic analysis of anosmic individuals has yet to confirm this possibility. Anosmias often target perception of distinct, noxious odorants. About 1 person in 1000 is insensitive to butyl mercaptan, the foul-smelling odorant released by skunks. More serious is the inability to

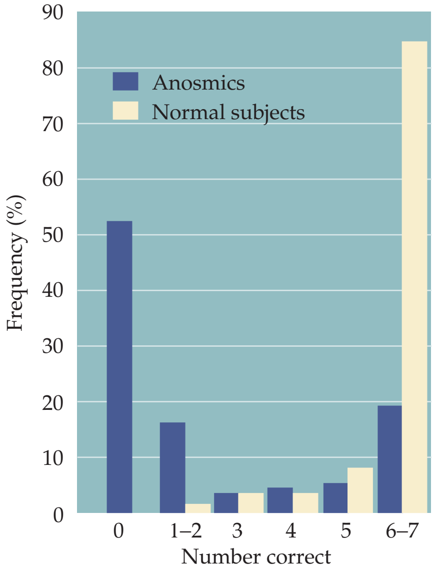


Figure 14.3 Anosmia is the inability to identify common odors. When subjects are presented with seven common odors (a test frequently used by neurologists), the vast majority of "normal" individuals can identify all seven odors correctly (in this case, baby powder, chocolate, cinnamon, coffee, mothballs, peanut butter, and soap). Some people, however, have difficulty identifying even these common odors. In this example, individuals previously identified as anosmics were presented with the same battery of odors, only a few could identify all of the odors (less than 15%), and more than half could not identify any of the odors. (After Cain and Gent, in Meiselman and Rivlin, 1986.)

detect hydrogen cyanide (1 in 10 people), which can be lethal, or ethyl mercaptan, the chemical added to natural gas to aid in the detection of gas leaks.

The ability to identify odors normally decreases with age. If otherwise healthy subjects are challenged to identify a large battery of common odorants, people between 20 and 40 years of age can typically identify about 50–75% of the odors, whereas those between 50 and 70 correctly identify only about 30–45% (Figure 14.4). A more radically diminished or distorted sense of smell can accompany eating disorders, psychotic disorders (especially schizophrenia), diabetes, taking certain medications, and Alzheimer's disease (all for reasons that remain obscure). Although the loss of human olfactory sensitivity is not usually a source of great concern, it can diminish the enjoyment of food and, if severe, can affect the ability to identify and respond appropriately to potentially dangerous odors such as spoiled food, smoke, or natural gas.

The neural substrates for odor processing in humans includes all of the structures identified anatomically as part of the olfactory pathway: the olfactory bulb, pyriform and orbital cortices, amygdala and hypothalamus are all clearly activated by presentation of odorants in functional magnetic resonance images (fMRI) of normal human subjects (Figure 14.1E). Although fMRI cannot resolve differences in the local activity elicited by most individual odors, some clear distinctions have been seen that support corresponding behavioral observations. Furthermore, the decline in olfactory ability with age mentioned above is matched by a decline in the level of activity in olfactory regions of the aging human brain.

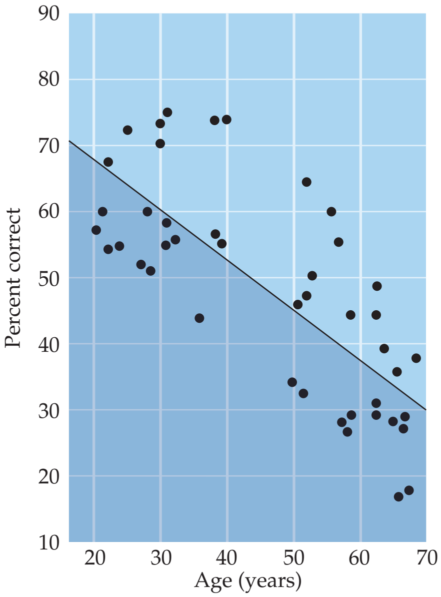


Figure 14.4 Normal decline in olfactory sensitivity with age. The ability to identify 80 common odorants declines markedly between 20 and 70 years of age. (After Murphy, 1986.)

Physiological and Behavioral Responses to Odorants

In addition to olfactory perceptions, odorants can elicit a variety of physiological responses. Examples are the visceral motor responses to the aroma of appetizing food (salivation and increased gastric motility) or to a noxious smell (gagging and, in extreme cases, vomiting). Olfaction can also influence reproductive and endocrine functions. Women housed in single-sex dormitories, for instance, have menstrual cycles that tend to be synchronized, a phenomenon that appears to be mediated by olfaction. Volunteers exposed to gauze pads from the underarms of women at different stages of their menstrual cycles also tend to experience synchronized menses, and this synchronization can be disrupted by exposure to gauze pads from men. Olfaction also influences mother–child interactions. Infants recognize their mothers within hours after birth by smell, preferentially orienting toward their mothers' breasts and showing increased rates of suckling when fed by their mother compared to being fed by other lactating females, or when presented experimentally with their mother's odor versus that of an unrelated female (see Chapter 23). By the same token, mothers can discriminate their own infant's odor when challenged with a range of odor stimuli from infants of similar age.

In other animals, including many mammals, species-specific odorants called **pheromones** play important roles in behavior, by influencing social, reproductive, and parenting behaviors (Box A). In rats and mice, odorants thought to be pheromones are detected by G-protein-coupled receptors located at the base of the nasal cavity in distinct, encapsulated chemosensory structures called **vomeronasal organs** (**VNOs**). In many mammals, VNOs project to the accessory olfactory bulb, which in turn projects to the hypothalamus (where reproductive activity is generally regulated; see Chapter 29). VNOs are found bilaterally in only 8% of adult humans, and there is no clear

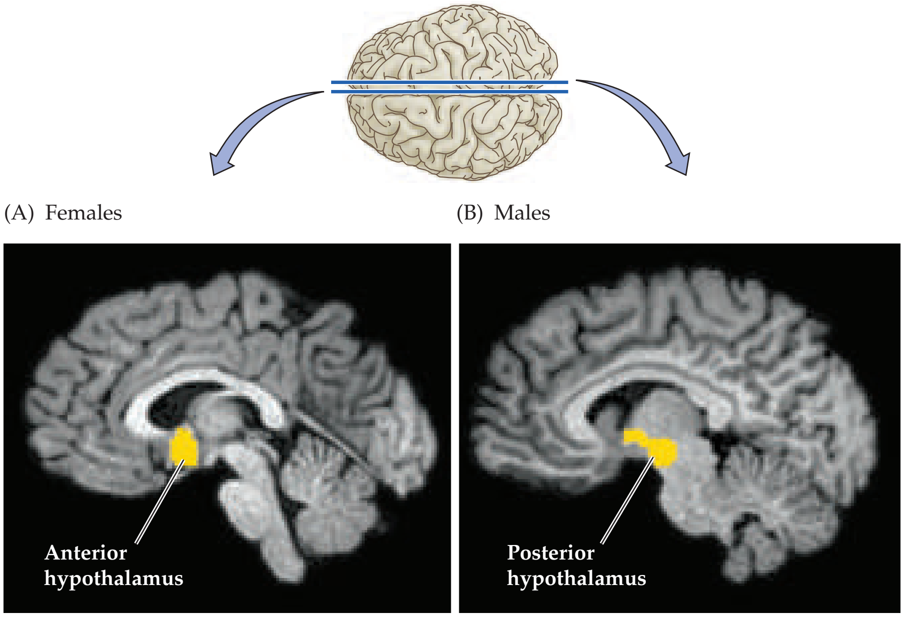


Figure 14.5 Differential patterns of activation in the hypothalamus of normal human female (right) and male (left) subjects after exposure to an estrogen- or androgen-containing odor mix. (From Savic et al., 2001.)

indication that these human structures have any significant function. The human genes encoding homologues of pheromone receptors expressed by VNO neurons in other mammals are mostly pseudogenes (i.e., the sequences have been mutated over the course of evolution so that these genes cannot be expressed). Thus, it is unlikely that human pheromone perception, if it exists, is mediated by the vomeronasal system, as is the case in other mammals. Nevertheless, recent observations suggest that exposure to androgen and estrogen-like compounds at concentrations below the level of conscious detection can elicit both behavioral responses and different patterns of brain activation in adult female and male human subjects (Figure 14.5). Thus, although most humans do not process pheromones by the vomeronasal system, other olfactory structures can evidently detect signals that may affect reproductive and other behaviors.

The Olfactory Epithelium and Olfactory Receptor Neurons

The transduction of olfactory information occurs in the olfactory epithelium, the sheet of neurons and supporting cells that lines approximately half of the nasal cavities. (The remaining surface is lined by respiratory epithelium, which lacks neurons and serves primarily as a protective surface.) The olfactory epithelium includes several cell types (Figure 14.6A). The most important of these is the **olfactory receptor neuron**, a bipolar cell that gives rise to a small-diameter, unmyelinated axon at its basal surface that transmits olfactory information centrally. At its apical surface, the receptor neuron gives rise to a single dendritic process that expands into a knoblike protrusion from which several microvilli, called **olfactory cilia**, extend into a thick layer of mucus. The mucus that lines the nasal cavity and controls the ionic milieu of the olfactory cilia is produced by secretory specializations (called Bowman's glands) distributed throughout the epithelium. When the mucus layer becomes thicker, as during a cold, olfactory acuity decreases significantly. Two other cell classes, basal cells and sustentacular (supporting) cells, are also

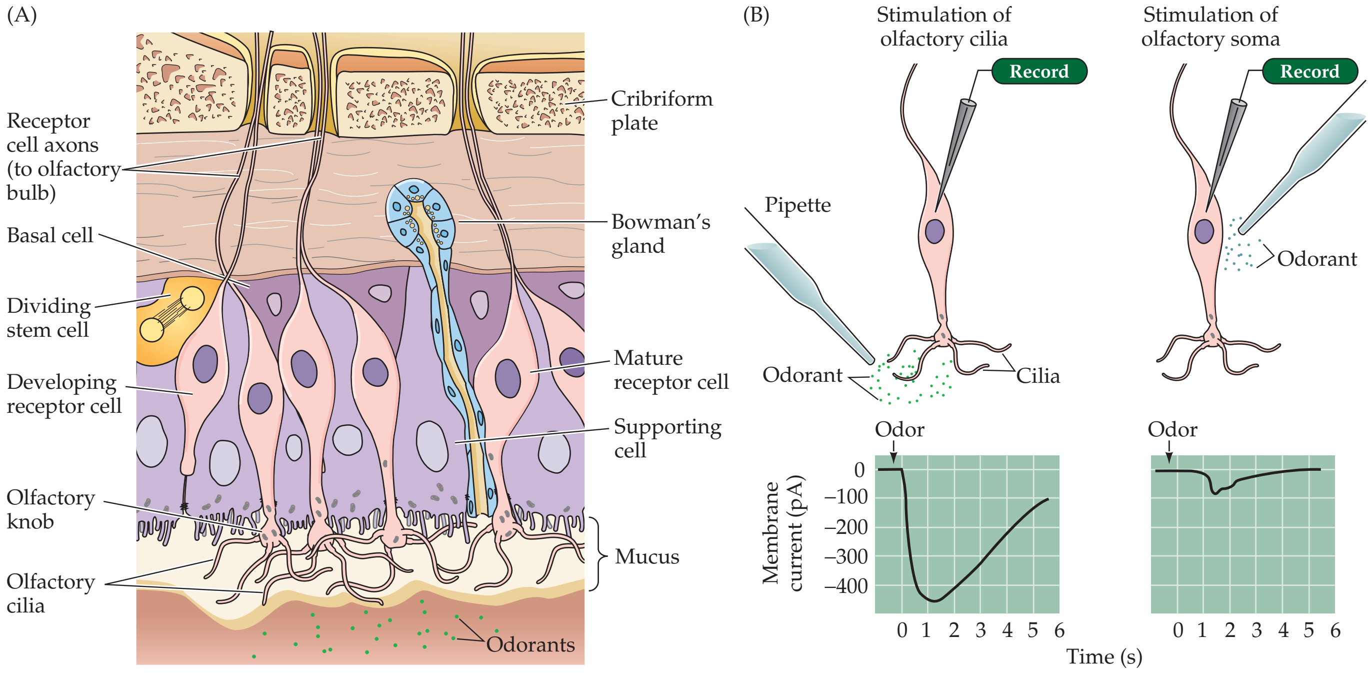

(A)
Receptor cell axons (to olfactory bulb)
Basal cell
Dividing stem cell
Developing receptor cell
Olfactory knob
Olfactory cilia
Cribriform plate
Bowman's gland
Mature receptor cell
Supporting cell
Mucus
Odorants
(B)
Stimulation of olfactory cilia
Record
Pipette
Odorant
Cilia
Stimulation of olfactory soma
Record
Odorant
Odor
Odor
Membrane current (pA)
0
−100
−200
−300
−400
0 1 2 3 4 5 6
0 1 2 3 4 5 6
Time (s)

Figure 14.6 Structure and function of the olfactory epithelium. (A) Diagram of the olfactory epithelium showing the major cell types: olfactory receptor neurons and their cilia, sustentacular cells (that detoxify potentially dangerous chemicals), and basal cells. Bowman's glands produce mucus. Nerve bundles of unmyelinated neurons and blood vessels run in the basal part of the mucosa (called the lamina propria). Olfactory receptor neurons are generated continuously from basal cells. (B) Generation of receptor potentials in response to odors takes place in the cilia of receptor neurons. Thus, odorants evoke a large inward (depolarizing) current when applied to the cilia (left), but only a small current when applied to the cell body (right). (A after Anholt, 1987; B after Firestein et al., 1991.)

present in the olfactory epithelium. This entire apparatus—mucus layer and epithelium with neural and supporting cells—is called the **nasal mucosa**.

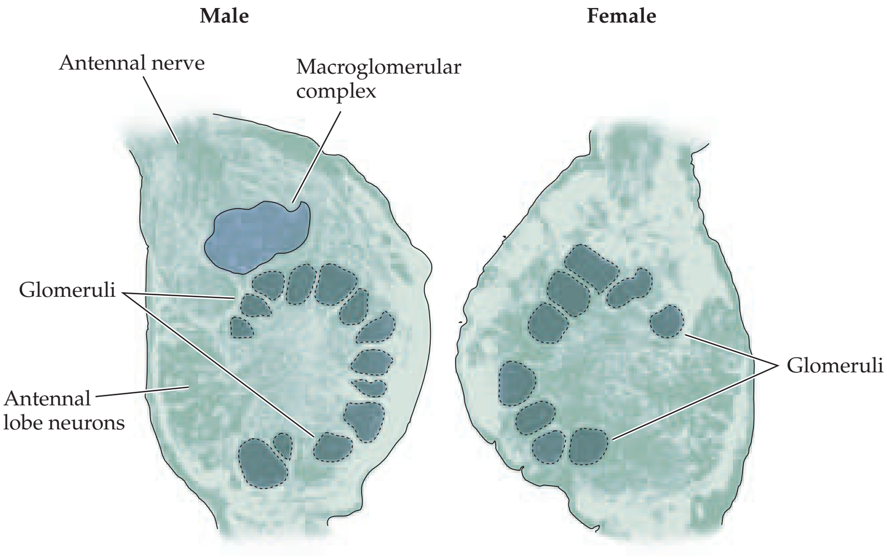
The superficial location of the nasal mucosa allows the olfactory receptor neurons direct access to odorant molecules. Another consequence, however, is that these neurons are exceptionally exposed. Airborne pollutants, allergens, microorganisms, and other potentially harmful substances subject the olfactory receptor neurons to more or less continual damage. Several mechanisms help maintain the integrity of the olfactory epithelium in the face of this trauma. The ciliated cells of the respiratory epithelium, a non-neural epithelium found at the most external aspect of the nasal cavity, warms and moistens the inspired air. In addition, glandular cells throughout the epithelium secrete mucus, which traps and neutralizes potentially harmful agents. In both the respiratory and olfactory epithelium, immunoglobulins are secreted into the mucus, providing an initial defense against harmful antigens, and the sustentacular cells contain enzymes (cytochrome P450s and others) that catabolize organic chemicals and other potentially damaging molecules that enter the nasal cavity. The ultimate solution to this problem, however, is to replace olfactory receptor neurons in a normal cycle of degeneration and regeneration. In rodents, the entire population of olfactory neurons is renewed every 6 to 8 weeks. This feat is accomplished by maintaining among the basal cells a population of precursors (stem cells) that divide to give rise to new receptor neurons (see Figure 14.6A). This naturally occurring regeneration of olfactory receptor cells provides an opportunity to investigate how neural precursor cells can successfully produce new neurons and reconstitute function in the mature central nervous system, a topic of broad clinical interest. Recent evidence suggests that many of the signaling molecules that influence neuronal differentiation, axon outgrowth, and synapse formation during development elsewhere in the nervous system (see Chapters 21 and 22) perform similar functions for regenerating olfactory

Box A
Olfaction, Pheromones, and Behavior in the Hawk Moth

Olfactory information guides essential behaviors in virtually all species. The importance of olfactory cues in reproductive behaviors has been particularly well characterized in the hawk moth, *Manduca sexta.* In *Manduca*, males identify potential mates by following a plume of pheromones exuded by the female. Similarly, the female uses an olfactory cue—a molecule made by tobacco plants—to identify an appropriate site to lay eggs. These olfactory functions in the moths are sexually dimorphic: Only males respond to female pheromones, and only females detect the olfactory stimulus from the tobacco plant needed for egg-laying.

These abilities are mediated by an olfactory system that shares some remarkable similarities with mammalian systems. Male and female moths have different olfactory receptor cells (and associated structures) on their antennae which generate receptor potentials in response to the female-specific pheromones or the tobacco plant odorants. These peripheral receptors project to olfactory recipient structures that are reminiscent of the mammalian olfactory bulb (see figure). The target structure in the moth—called the antennal lobe—is comprised of an array of iterated circuits that are referred to as glomeruli and are surprisingly similar in both structure and function to glomeruli in the mammalian olfactory bulb. In males, the antennal receptor neurons sensitive to the female pheromone project to a distinct subset of glomeruli called the macroglomerular complex. These glomeruli are specifically active in the presence of female pheromone and, if absent, prevent any behavioral response to the female scent. Finally, the development of these sexually dimorphic central circuits is controlled by the periphery. If a male antennae is transplanted to a genotypically female moth, a macroglomerular complex develops in the antennal lobe. The female-specific pheromone has been identified, as have several receptor molecules specifically associated with the male or female olfactory pathway, respectively. Not surprisingly, pheromone receptors in the male are members of a special class of seven transmembrane odorant receptors found in other invertebrates and vertebrates.

The matching of identified glomeruli with receptor cells expressing specific receptor molecules may be a general rule in olfactory systems. If so, the neurobiology of a sexually dimorphic olfactory behavior in the moth provides an ideal model system in which to study chemosensory processing of specific odorants.



Male and female olfactory glomeruli in the antennal lobe are specialized for odorant-mediated behaviors. The male-specific macroglomerular complex (MCG) is essential for processing the female pheromone.

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receptor neurons in the adult. Understanding how the new olfactory receptor neurons differentiate into functional neurons, extend axons to the brain, and reestablish appropriate functional connections is obviously relevant to stimulating the regeneration of functional connections elsewhere in the brain after injury or disease (see Chapter 24).

The Transduction of Olfactory Signals

The cellular and molecular machinery for olfactory transduction is located in the cilia of olfactory receptor neurons (see Figure 14.6B). Despite their external appearance, olfactory cilia do not have the cytoskeletal features of motile cilia (the so-called 9 + 2 arrangement of microtubules). Odorant transduction begins with odorant binding to specific receptors on the external surface of cilia. Binding may occur directly, or by way of proteins in the mucus (called odorant binding proteins) that sequester the odorant and are thought to shuttle it to the receptor. Several additional steps then generate a receptor potential by opening ion channels. In mammals, the principal pathway involves cyclic nucleotide-gated ion channels, similar to those found in rod photoreceptors (see Chapter 10). The olfactory receptor neurons express an olfactory-specific G-protein (G_{olf}), which activates an olfactory-specific adenylate cyclase (Figure 14.7A). Both of these proteins are restricted to the knob and cilia, consistent with the idea that odor transduction occurs in these portions of the olfactory receptor neuron. Stimulation of odorant receptor molecules leads to an increase in cyclic AMP (cAMP) which opens channels that permit Na^+ and Ca^{2+} entry (mostly Ca^{2+}), thus depolarizing the neuron. This depolarization, amplified by a Ca^{2+}-activated Cl^- current, is conducted passively from the cilia to the axon hillock region of the olfactory receptor neuron, where action potentials are generated and transmitted to the olfactory bulb.

Olfactory receptor neurons are especially efficient at extracting a signal from chemosensory noise. Fluctuations in the cAMP concentration in an olfactory receptor neuron could, in theory, cause the receptor cell to be activated in the absence of odorants. Such nonspecific responses do not occur, however, because the cAMP-gated channels are blocked at the resting potential by the high Ca^{2+} and Mg^{2+} concentrations in mucus. To overcome this

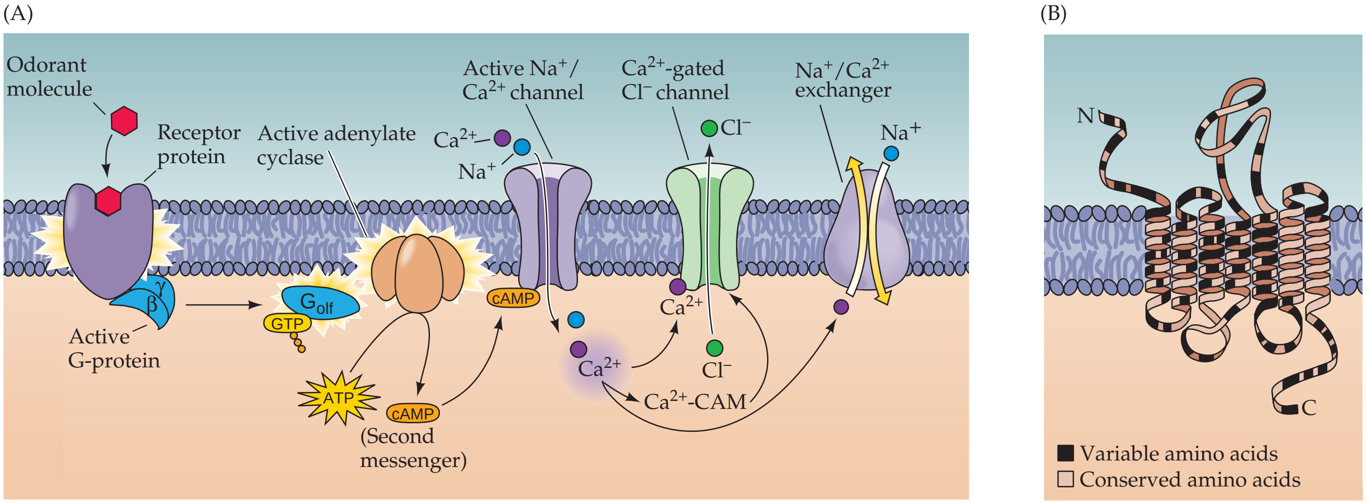


Figure 14.7 Olfactory transduction and olfactory receptor molecules. (A) Odorants in the mucus bind directly (or are shuttled via odorant binding proteins) to one of many receptor molecules located in the membranes of the cilia. This association activates an odorant-specific G-protein (G_{olf}) that, in turn, activates an adenylate cyclase, resulting in the generation of cyclic AMP (cAMP). One target of cAMP is a cation-selective channel that, when open, permits the influx of Na^+ and Ca^{2+} into the cilia, resulting in depolarization. The ensuing increase in intracellular Ca^{2+} opens Ca^{2+}-gated Cl^- channels that provide most of the depolarization of the olfactory receptor potential. The receptor potential is reduced in magnitude when cAMP is broken down by specific phosphodiesterases to reduce its concentration. At the same time, Ca^{2+} complexes with calmodulin (Ca^{2+}-CAM) and binds to the channel, reducing its affinity for cAMP. Finally, Ca^{2+} is extruded through the Ca^{2+}/Na^+ exchange pathway. (B) The generic structure of putative olfactory odorant receptors. These proteins have seven transmembrane domains, plus a variable cell surface region and a cytoplasmic tail that interacts with G-proteins. As many as 1000 genes encode proteins of similar inferred structure in several mammalian species, including humans. Each gene presumably encodes an odorant receptor that detects a particular set of odorant molecules. (Adapted from Menini, 1999.)

voltage-dependent block, several channels must be opened at once. This requirement ensures that olfactory receptor neurons fire only in response to stimulation by odorants. Moreover, changes in the odorant concentration change the latency of response, the duration of the response, and/or the firing frequency of individual neurons, each of which provides additional information about the environmental circumstances to the central stations in the system.

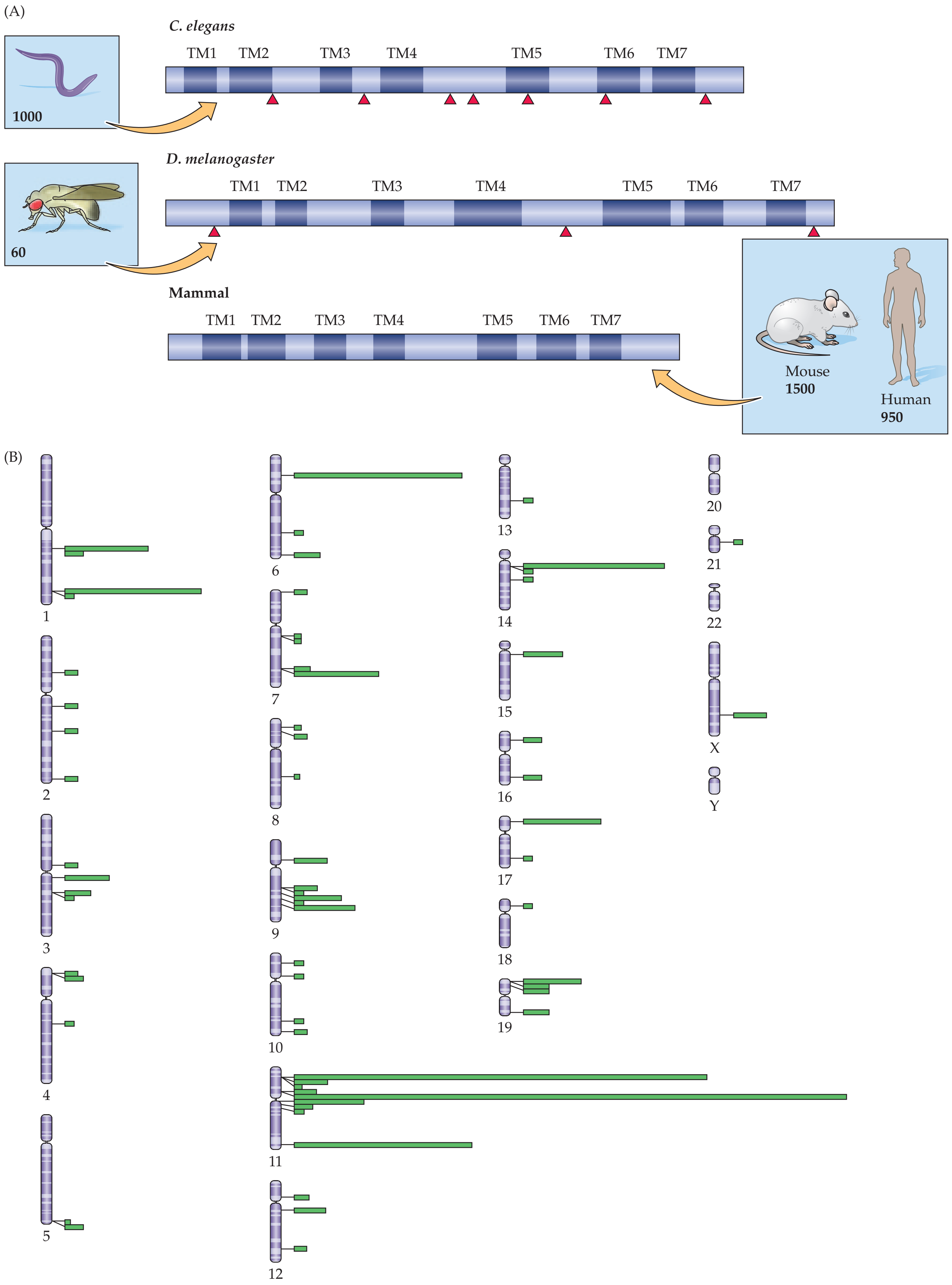
Finally, like other sensory receptors, olfactory neurons adapt in the continued presence of a stimulus. Adaptation is apparent subjectively as a decreased ability to identify or discriminate odors during prolonged exposure (e.g., decreased awareness of being in a “smoking” room at a hotel as more time is spent there). Physiologically, olfactory receptor neurons indicate adaptation by a reduced rate of action potentials in response to the continued presence of an odorant. Adaptation occurs because of (1) increased Ca^{2+} binding by calmodulin, which decreases the sensitivity of the channel to cAMP; and (2) the extrusion of Ca^{2+} through the activation of Na^+/Ca^{2+} exchange proteins, which reduces the depolarizing potential from Ca^{2+} activated Cl^- channels.

Odorant Receptors

Olfactory receptor molecules (Figure 14.7B) are homologous to a large family of other G-protein-linked receptors that includes β-adrenergic receptors, muscarinic acetylcholine receptors, and the photopigments rhodopsin and the cone opsins. In all invertebrates and vertebrates examined thus far, odorant receptor proteins have seven membrane-spanning hydrophobic domains, potential odorant binding sites in the extracellular domain of the protein, and the usual ability to interact with G-proteins at the carboxyl terminal region of their cytoplasmic domain. The amino acid sequences for these molecules also show substantial variability, particularly in regions that code for the membrane-spanning domains. The specificity of olfactory signal transduction is presumably the result of this molecular variety of odorant receptor molecules present in the nasal epithelium.

The numbers of odorant receptor genes in humans and other animals also varies widely (Figure 14.8A). Analysis of the complete human genome sequence has idenfied approximately 950 odorant receptor genes. In rodents (the mouse has been the animal of choice for such studies because of its well-established genetics), genome analysis has identified about 1500 different odorant receptor genes. Thus, in mammals, odorant receptors are the largest known gene family, representing between 3 and 5% of all genes.

Figure 14.8 Odorant receptor genes. (A) The number of genes that encode odorant receptors in *C. elegans*, *Drosophila*, mice, and humans are indicated in the appropriate boxes. In each instance, we see the seven transmembrane domains characteristic of G-protein-coupled receptors (dark regions); however, the comparative size of each domain, plus the intervening cytoplasmic or cell surface domains, varies from species to species. In addition, splice sites (arrowheads) reflect introns in the genomic sequences of the two invertebrates; in contrast, the genes for mammalian odorant receptors lack introns. (B) The distribution of odorant receptor genes in the human genome. The relative number of genes is indicated by the green bar extending toward the right from each chromosome. There are odorant receptor genes on each human chromosome except for chromosomes 20, 22, and the Y chromosome. (A after Dryer, 2000; B after Mombaerts, 2001.) ▶


(A)
C. elegans
TM1 TM2 TM3 TM4 TM5 TM6 TM7
D. melanogaster
TM1 TM2 TM3 TM4 TM5 TM6 TM7
Mammal
TM1 TM2 TM3 TM4 TM5 TM6 TM7
Mouse
1500
Human
(B)
X
Y

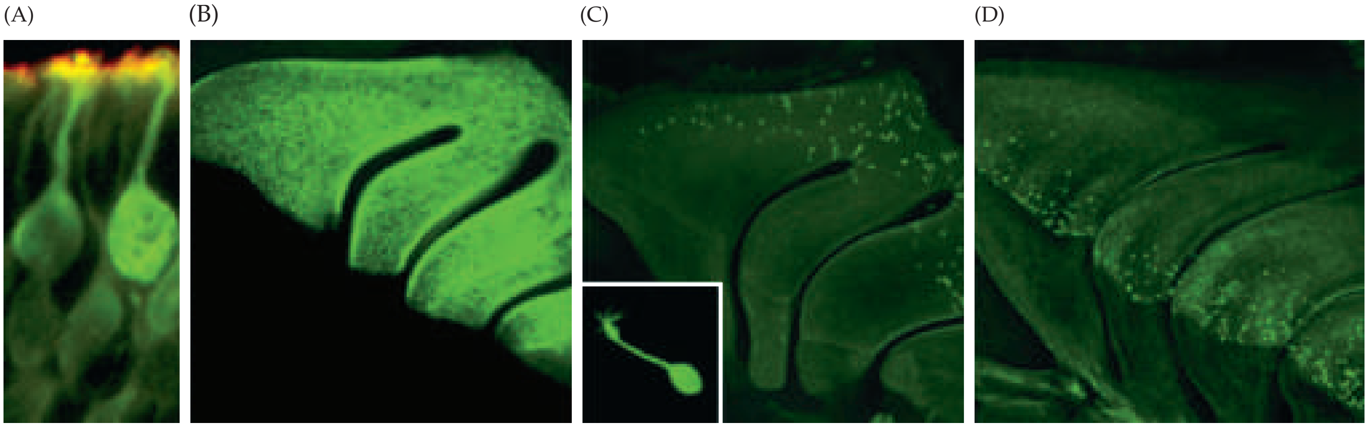


Figure 14.9 Odorant receptor gene expression. (A) Individual olfactory receptor neurons labeled immunohistochemically with the olfactory marker protein OMP (green label; OMP is selective for all olfactory receptor neurons) and the olfactory receptor neuron-specific adenylyl cyclase III (red label) that is limited to cilia. The labels are in register with the segregation of signal transduction components to this domain. (B) The distribution of OMP-expressing olfactory receptor neurons in the nasal epithelium of an adult mouse, demonstrated with a reporter transgene. The protuberances oriented diagonally from left to right represent individual turbinates within the olfactory epithelium. The remaining bony and soft-tissue structures of the nose have been dissected away. (C) The distribution of olfactory receptor neurons expressing the I7 odorant receptor. These cells are restricted to a distinct domain or zone in the epithelium. The inset photo shows that odorant receptor-expressing cells are indeed cilia-bearing olfactory receptor neurons. (D) Olfactory receptor neurons expressing the M81 odorant receptor are limited to a zone that is completely distinct from that of the I7 receptor. (A courtesy of C. Balmer and A. LaMantia; B–D from Bozza et al., 2002.)

Additional sequence analysis of human and mouse odorant receptor genes, however, suggests that many—around 60% in human and 20% in mouse—are not transcribed. Thus, the numbers of functional odorant receptor proteins are estimated to be around 400 in humans and 1200 in mice. Similar analysis of complete genome sequences from the worm *C. elegans* and the fruit fly *D. melanogaster* indicate that there are approximately 1000 odorant receptor genes in the worm, but only about 60 in the fruit fly. The significance of these quite different numbers of odorant receptor genes is not known.

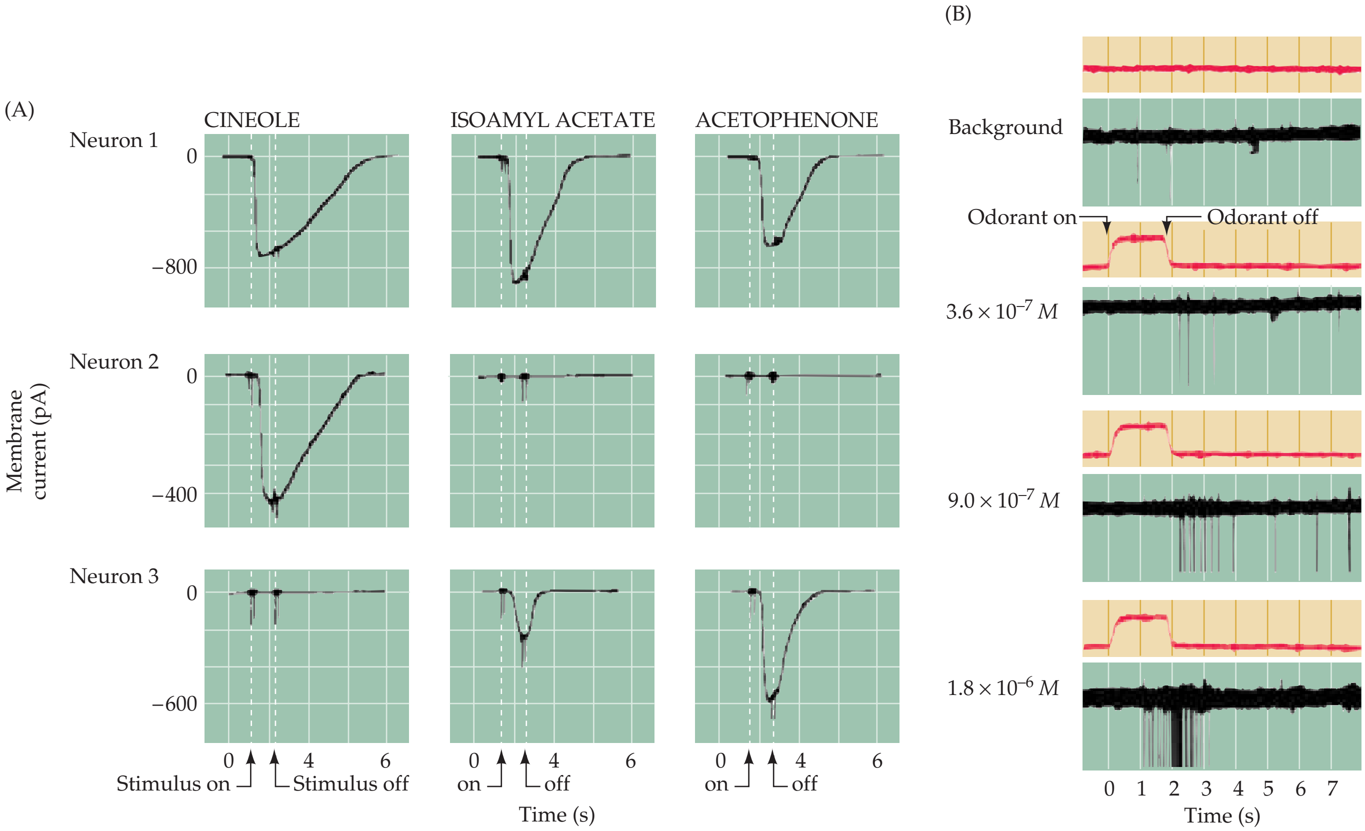
Due to the large number of odorant receptor genes, expression in olfactory receptor neurons has only been confirmed for a limited subset (Figure 14.9). Messenger RNAs for different odorant receptor genes are expressed in subsets of olfactory neurons that occur in bilaterally symmetric patches of olfactory epithelium. Additional evidence for odorant receptor gene expression comes from molecular genetic experiments where reporter proteins like β-galactosidase or green fluorescent protein have been inserted into odorant receptor gene loci. In these experiments (done primarily in mice and fruit flies) expression of the reporter protein is limited to individual olfactory receptor neurons and their processes in distinct regions of the olfactory epithelium. Genetic as well as cell biological analysis shows that each olfactory receptor neuron expresses only one or at most a few odorant receptor genes. Thus, different odors must activate molecularly and spatially distinct subsets of olfactory receptor neurons.

Olfactory Coding

Like other sensory receptor cells, individual olfactory receptor neurons are sensitive to a subset of stimuli. Presumably, depending on the particular olfactory receptor molecules they express, some olfactory receptor neurons exhibit marked selectivity to a particular chemical stimulus, whereas others are activated by a number of different odorant molecules (Figure 14.10A). In addition, olfactory receptor neurons can exhibit different thresholds for a particular odorant. That is, receptor neurons that are inactive at concentrations sufficient to stimulate some neurons are activated when exposed to higher concentrations of the same odorant. These characteristics suggest why the perception of an odor can change as a function of its concentration (Figure 14.10B). The relationship between physiological tuning of single olfactory receptor neurons and chemical specificity of single odorant receptor molecules remains unclear. At present, there is only one mammalian odorant receptor molecule, the I7 receptor, whose ligand specificity has been evaluated. This receptor has a high affinity for the aldehyde *n*-octanal, as well as some affinity for related molecules. While most of the molecular analysis has been done in rodents, humans can perceive *n*-octanal—it smells like freshly cut grass. Thus, it is possible that ligands for other individual odorant receptors eventually will be found, and these ligands will correspond to perceptually relevant odors.

How olfactory receptor neurons represent the identity and concentration of a given odorant is a complex issue that is unlikely to be explained solely by the properties of the primary receptor neurons. Nevertheless, neurons with specific receptors are located in particular parts of the olfactory epithelium. As in other sensory systems, the topographical arrangement of receptor neurons expressing distinct odorant receptor molecules is referred to as **space coding**, although the meaning of this phrase in the olfactory system is much less clear than in vision, where a topographical map correlates with visual space. The coding of olfactory information also has a temporal dimension. Sniffing, for instance, is a periodic event that elicits trains of action potentials and synchronous activity in populations of neurons. Information conveyed by timing is called **temporal coding** and occurs in a variety of species (Box B). The contribution of spatial or temporal coding to olfactory perception is not yet known.

Figure 14.10 Responses of olfactory receptor neurons to selected odorants. (A) Neuron 1 responds similarly to three different odorants. In contrast, neuron 2 responds to only one of these odorants. Neuron 3 responds to two of the three stimuli. The responses of these receptor neurons were recorded by whole-cell patch clamp recording; downward deflections represent inward currents measured at a holding potential of –55 mV. (B) Responses of a single olfactory receptor neuron to changes in the concentration of a single odorant, isoamyl acetate. The upper trace in each panel (red) indicates the duration of the odorant stimulus; the lower trace the neuronal response. The frequency and number in each panel of action potentials increases as the odorant concentration increases. (A after Firestein, 1992; B after Getchell, 1986.)



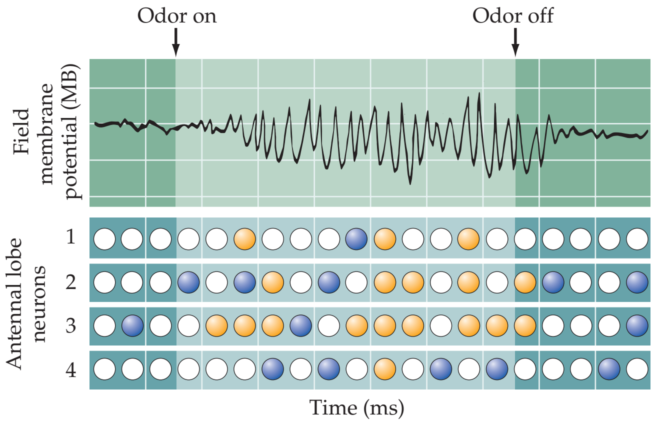
Box B

Temporal "Coding" of Olfactory Information in Insects

Most studies of olfaction in mammals have emphasized the spatial patterns of receptors in the nose and glomeruli in the bulb that are activated by specific odorants. However, beginning with Edgar Adrian's study of the hedgehog olfactory bulb in 1942, odor-induced temporal oscillations have been described in species as diverse as turtles and primates. A variety of functions have been proposed for these oscillatory phenomena, including identification of odor type and perception of odor intensity.

Gilles Laurent and colleagues at California Institute of Technology have recently found that olfaction in insects does show an important temporal component related to behavior. By recording intracellularly from neurons in the antennal lobe in crickets (a structure analogous to the olfactory bulb in mammals; see also Box A) and extracellularly in the mushroom body (analogous to the mammalian pyriform cortex), they found that the projection neurons in the antennal lobe (corresponding to mammalian mitral cells) respond to a given odor with a variety of temporal patterns that differ from odor to odor but are reproducible for the same odor. The figure here shows a schematic representation of these temporal aspects of the odor response of four such projection neurons. The upper panel shows a local field potential recording from the mushroom body (MB) that represents the synaptic activity of many neurons. During presentation of the odor, a pattern of activity is generated by the synchronized firing of many projection neurons. Interestingly, this oscillation at 20–30 Hz is independent of the odor. Each small sphere in the lower panels represents the state of one of the four neurons before, during, and after the application of an odorant. White balls represents a silent or inhibited state, blue balls an active but unsynchronized state, and orange balls an active *and* synchronized state. The figure shows that at different times during the odor presentation, various neurons are in synchrony and thus contribute at different times to the field potential recorded in the mushroom body. Desynchronizing the neurons has the effect of eliminating the 20–30 Hz oscillation. Desynchronization does not modify the insects' responses to odors, but eliminates their ability to distinguish among similar odors.

These observations suggest that coherent firing among neurons is an important component of olfactory processing in this species, and raise the possibility that temporal coding is a more important aspect of mammalian olfaction than has so far been imagined.



Temporal coding of olfactory information in insects. (From Laurent et al., 1996.)

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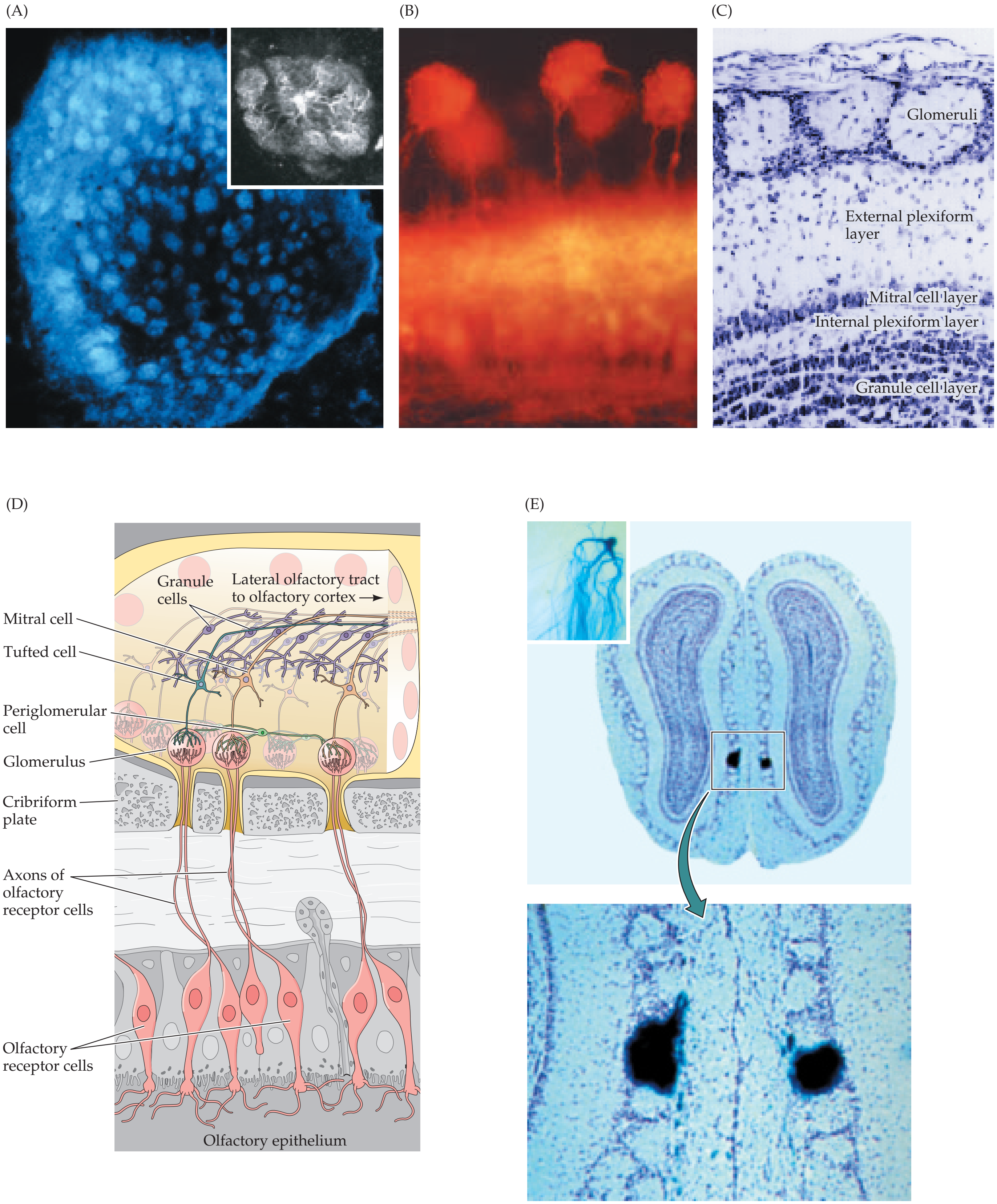
The Olfactory Bulb

Transducing and relaying odorant information centrally from olfactory receptor neurons are only the first steps in processing olfactory signals. As the olfactory receptor axons leave the olfactory epithelium, they coalesce to form a large number of bundles that together make up the **olfactory nerve** (cranial nerve I). Each olfactory nerve projects ipsilaterally to the **olfactory bulb** on that side, which lies on the ventral anterior aspect of the ipsilateral forebrain. The most distinctive feature of the olfactory bulb is an array of more or less spherical accumulations of neuropil 100–200 µm in diameter called **glomeruli,** which lie just beneath the surface of the bulb and receive the primary olfactory axons (Figure 14.11A–C). Although a remarkable feature of the mammalian olfactory bulb, glomeruli are found in central nervous system regions that process olfaction in most animals, including insects like *Drosophila* (Figure 14.11A inset) and the moth (see Box A). In vertebrates, the olfactory bulb comprises several cell and neuropil layers that receive, process, and relay olfactory information.

Within each glomerulus, the axons of the receptor neurons contact the apical dendrites of **mitral cells,** which are the principal projection neurons of the olfactory bulb. The cell bodies of the mitral cells are located in a distinct layer deep to the olfactory glomeruli and, in adults, extend a primary dendrite into a single glomerulus, where the dendrite gives rise to an elaborate tuft of branches onto which the primary olfactory axons synapse (Figure 14.11B and D). Each glomerulus in the mouse (where glomerular connectivity has been studied quantitatively) includes the apical dendrites of approximately 25 mitral cells, which receive innervation from approximately 25,000 olfactory receptor axons. This degree of convergence presumably serves to increase the sensitivity of mitral cells to ensure odor detection, and to increase the signal strength by averaging out uncorrelated noise. Each glomerulus also includes dendritic processes from two other classes of local circuit neurons: tufted cells and periglomerular cells (approximately 50 tufted cells and 25 periglomerular cells contribute to each glomerulus). Although it is generally assumed that these neurons sharpen the sensitivity of individual glomeruli, their function is unclear.

Finally, granule cells, which constitute the innermost layer of the vertebrate olfactory bulb, synapse primarily on the basal dendrites of mitral cells within the external plexiform layer (Figure 14.11C,D). These cells lack an identifiable axon, and instead make dendrodendritic synapses on mitral cells. Granule cells are thought to establish local lateral inhibitory circuits as well as participating in synaptic plasticity in the olfactory bulb. In addition, olfactory granule cells and periglomerular cells are among the few classes of neurons in the forebrain that can be replaced throughout life. Granule cell precursors are maintained in a region outside of the olfactory bulb, within the cells that line the ventricles of the cortical hemispheres called the anterior subventricular zone (see Chapter 24). The neural stem cells in this region can give rise to postmitotic cells that then migrate through a region referred to as the rostral migratory stream that spans the territory between the frontal cortex and the olfactory bulb. Once these migrating neurons arrive in the olfactory bulb, they can differentiate into either mature granule or periglomerular cells. Although it is tempting to speculate about the functional significance of this ongoing generation of granule cells, little is known about how these newly generated cells influence olfactory function or odor perception.

Bilaterally symmetrical subsets of glomeruli in the olfactory bulb (Figure 14.11E) receive input from olfactory receptor neurons that express distinct odorant receptor molecules. Thus, there is a special zone-to-zone projection between individual glomeruli in the olfactory bulb and groups of olfactory receptor neurons. As already mentioned, however, there is no obvious systematic representation in this arrangement as there is, for example, in the somatic sensory or visual systems. Rather, there is an affinity between widely distributed cells in the olfactory epithelium and a limited ensemble


(A)
(B)
(C)
Glomeruli
External plexiform layer
Mitral cell layer
Internal plexiform layer
Granule cell layer
(D)
Granule cells
Lateral olfactory tract to olfactory cortex
Mitral cell
Tufted cell
Periglomerular cell
Glomerulus
Cribriform plate
Axons of olfactory receptor cells
Olfactory receptor cells
Olfactory epithelium
(E)

◀ **Figure 14.11** The organization of the mammalian olfactory bulb. (A) When the bulb is viewed from its dorsal surface (visualized here in a living mouse in which the overlying bone has been removed), olfactory glomeruli can be seen. The dense accumulation of dendrites and synapses that constitute glomeruli are stained here with a vital fluorescent dye that recognizes neuronal processes. The inset shows a similar arrangement of glomeruli in the mushroom body (the equivalent of the olfactory bulb) in *Drosophila*. (B) Among the major neuronal components of each glomerulus are the apical tufts of mitral cells, which project to the pyriform cortex and other bulb targets (see Figure 14.1C). In this image of a coronal section through the bulb, they have been labeled retrogradely by placing the lipophilic tracer Di-I in the lateral olfactory tract. (C) The cellular structure of the olfactory bulb, shown in a Nissl-stained coronal section. The five layers of the bulb are indicated. The glomerular layer includes the tufts of mitral cells, the axon terminals of olfactory receptor neurons, and periglomerular cells that define the margins of each glomerulus. The external plexiform layer is made up of lateral dendrites of mitral cells, cell bodies and lateral dendrites of tufted cells, and dendrites of granule cells that make dendrodendritic synapses with the other dendritic elements. The mitral cell layer is defined by the cell bodies of mitral cells, and mitral cell axons are found in the internal plexiform layer. Finally, granule cell bodies are densely packed into the granule cell layer. (D) Diagram of the laminar and circuit organization of the olfactory bulb, shown in a cutaway view from its medial surface. Olfactory receptor cell axons synapse with mitral cell apical dendritic tufts and periglomerular cell processes within glomeruli. Granule cells and mitral cell lateral dendrites constitute the major synaptic elements of the external plexiform layer. (E) Axons from olfactory receptor neurons that express a particular odorant receptor gene converge on a small subset of bilaterally symmetrical glomeruli. These glomeruli, indicated in the boxed area in the upper panel, are shown at higher magnification in the lower panel. The projections from the olfactory epithelium have been labeled by a reporter transgene inserted by homologous recombination ("knocked in") into the genetic locus that encodes the particular receptor. (A from LaMantia et al., 1992; B,C from Pomeroy et al., 1990; E from Mombaerts et al., 1996.)

of target glomeruli. This arrangement suggests that individual glomeruli respond specifically (or at least selectively) to distinct odorants. Many investigations have confirmed the selective (but not uniquely specific) responsiveness of glomeruli to particular odorants using electrophysiological methods, voltage-sensitive dyes, and, most recently, intrinsic signals that depend on blood oxygenation (Figure 14.12). Such studies have also shown that increasing the odorant concentration increases the activity of individual glomeruli, as well as the number of glomeruli activated. While the exact mechanism by which these distributed patterns of activity represent odor quality and concentration remains unclear, one useful metaphor is to consider the sheet of glomeruli in the olfactory bulb as a bank of lights on a movie marquee: the spatial distribution of active and inactive glomeruli provides a message that is unique for a given odorant at a particular concentration.

Central Projections of the Olfactory Bulb

Glomeruli in the olfactory bulb are the sole target of olfactory receptor neurons, and thus the only relay—via the axons of mitral and tufted cells—for olfactory information from the periphery to the rest of the brain. The mitral cell axons form a bundle—the **lateral olfactory tract**—that projects to the accessory olfactory nuclei, the olfactory tubercle, the entorhinal cortex, and portions of the amygdala (see Figure 14.1A). The major target of the olfactory tract is the three-layered **pyriform cortex** in the ventromedial aspect of

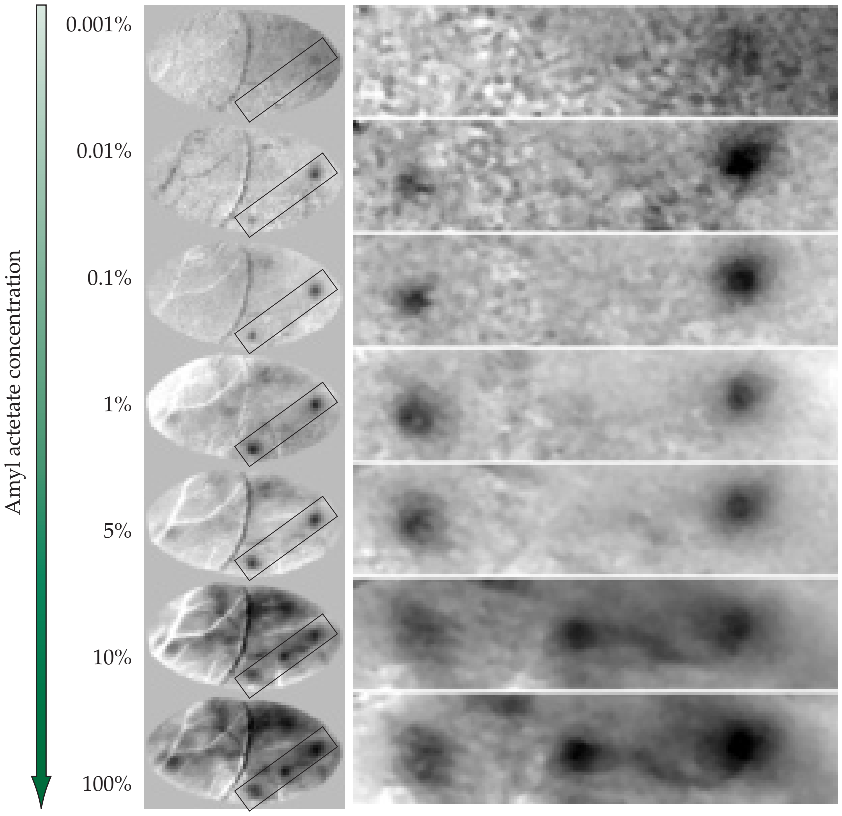


Figure 14.12 Glomerular activity recorded by optical imaging (see Box C in Chapter 11). Dorsal surface of the olfactory bulb in a living rat monitored as increasing concentrations of amyl acetate are presented to the animal. The higher the concentration, the more intense the activity in the particular glomeruli that respond to the odor. The column at left shows the entire dorsal surface of the olfactory bulb; the column at right shows a higher magnification of the individual glomeruli (indicated by the box in the left-hand column). (From Rubin and Katz, 1999.)

the temporal lobe near the optic chiasm. Neurons in pyriform cortex respond to odors, and mitral cell inputs from glomeruli receiving odorant receptor-specific projections remain partially segregated. The further processing that occurs in this region, however, is not well understood.

The axons of pyramidal cells in the pyriform cortex project in turn to several thalamic and hypothalamic nuclei and to the hippocampus and amygdala. Some neurons from pyriform cortex also innervate a region in the orbitofrontal cortex comprising multimodal neurons that respond to olfactory and gustatory stimuli. Information about odors thus reaches a variety of forebrain regions, allowing olfactory cues to influence cognitive, visceral, emotional, and homeostatic behaviors

The Organization of the Taste System

The taste system, acting in concert with the olfactory and trigeminal systems, indicates whether food should be ingested. Once in the mouth, the chemical constituents of food interact with receptors on **taste cells** located in epithelial specializations called **taste buds** in the tongue. The taste cells transduce these stimuli and provide additional information about the identity, concentration, and pleasant or unpleasant quality of the substance. This information also prepares the gastrointestinal system to receive food by causing salivation and swallowing (or gagging and regurgitation if the substance is unpleasant). Information about the temperature and texture of food is transduced and relayed from the mouth via somatic sensory receptors from the trigeminal and other sensory cranial nerves to the thalamus and somatic sensory cortices (see Chapters 8 and 9). Of course, food is not simply eaten for nutritional value; "taste" also depends on cultural and psychological factors. How else can one explain why so many people enjoy consuming hot peppers or bitter-tasting liquids such as beer?

Like the olfactory system, the taste system includes both peripheral receptors and a number of central pathways (Figure 14.13). Taste cells (the peripheral receptors) are found in taste buds distributed on the dorsal surface of the tongue, soft palate, pharynx, and the upper part of the esophagus (Figure 14.13A; see also Figure 14.14). These cells make synapses with primary sensory axons that run in the chorda tympani and greater superior petrosal branches of the facial nerve (cranial nerve VII), the lingual branch of the glossopharyngeal nerve (cranial nerve IX), and the superior laryngeal branch

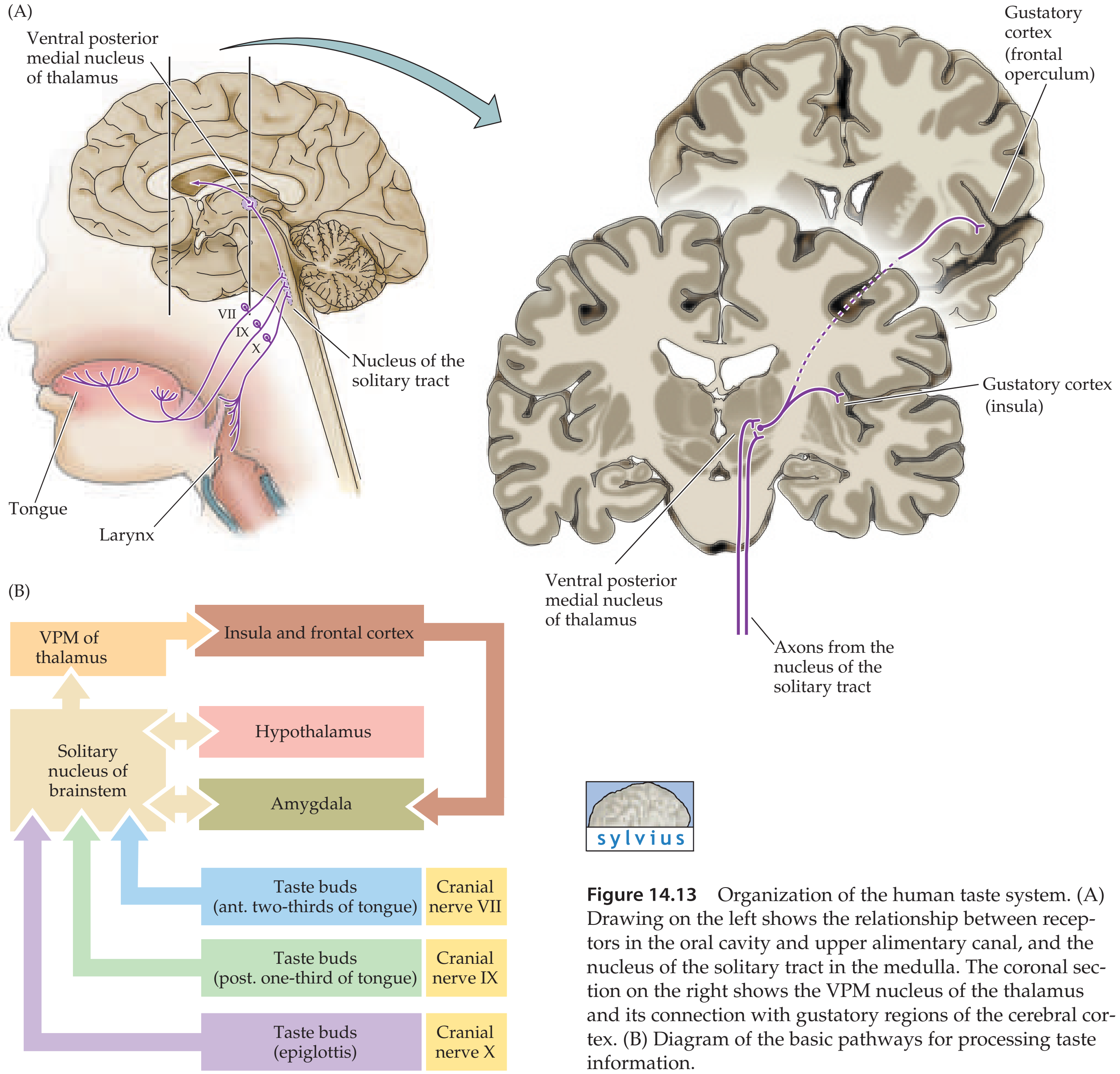

(A)
Ventral posterior medial nucleus of thalamus
VII
IX
X
Nucleus of the solitary tract
Tongue
Larynx
Gustatory cortex (frontal operculum)
Gustatory cortex (insula)
Ventral posterior medial nucleus of thalamus
Axons from the nucleus of the solitary tract
(B)
VPM of thalamus
Insula and frontal cortex
Hypothalamus
Solitary nucleus of brainstem
Amygdala
Taste buds (ant. two-thirds of tongue)
Cranial nerve VII
Taste buds (post. one-third of tongue)
Cranial nerve IX
Taste buds (epiglottis)
Cranial nerve X

Figure 14.13 Organization of the human taste system. (A) Drawing on the left shows the relationship between receptors in the oral cavity and upper alimentary canal, and the nucleus of the solitary tract in the medulla. The coronal section on the right shows the VPM nucleus of the thalamus and its connection with gustatory regions of the cerebral cortex. (B) Diagram of the basic pathways for processing taste information.

of the vagus nerve (cranial nerve X) to innervate the taste buds in the tongue, palate, epiglottis, and esophagus, respectively (see Appendix A for a review of the cranial nerves). The central axons of these primary sensory neurons in the respective cranial nerve ganglia project to rostral and lateral regions of the **nucleus of the solitary tract** in the medulla (Figure 14.13B), which is also known as the **gustatory nucleus** of the solitary tract complex (recall that the posterior region of the solitary nucleus is the main target of afferent visceral sensory information related to the sympathetic and parasympathetic divisions of the visceral motor system; see Chapter 20).

The distribution of these cranial nerves and their branches in the oral cavity is topographically represented along the rostral–caudal axis of the rostral portion of the gustatory nucleus; the terminations from the facial nerve are rostral, the glossopharyngeal are in the mid-region, and those from the vagus nerve are more caudal in the nucleus. Integration of taste and visceral sensory information is presumably facilitated by this arrangement. The caudal part of the nucleus of the solitary tract also receives innervation from subdiaphragmatic branches of the vagus nerve, which control gastric motility. Interneurons connecting the rostral and caudal regions of the nucleus represent the first interaction between visceral and gustatory stimuli. This close relationship of gustatory and visceral information makes good sense, since an animal must quickly recognize if it is eating something that is likely to make it sick, and respond accordingly.

Axons from the rostral (gustatory) part of the solitary nucleus project to the ventral posterior complex of the thalamus, where they terminate in the medial half of the **ventral posterior medial nucleus**. This nucleus projects in turn to several regions of the cortex, including the anterior insula in the temporal lobe and the operculum of the frontal lobe. There is also a secondary cortical taste area in the caudolateral orbitofrontal cortex, where neurons respond to combinations of visual, somatic sensory, olfactory, and gustatory stimuli. Interestingly, when a given food is consumed to the point of satiety, specific orbitofrontal neurons in the monkey diminish their activity to that tastant, suggesting that these neurons are involved in the motivation to eat (or not to eat) particular foods. Finally, reciprocal projections connect the nucleus of the solitary tract via the pons to the hypothalamus and amygdala (see Figure 14.13B). These projections presumably influence appetite, satiety, and other homeostatic responses associated with eating (recall that the hypothalamus is the major center governing homeostasis; see Chapter 20).

Taste Perception in Humans

Most taste stimuli are nonvolatile, hydrophilic molecules soluble in saliva. Examples include salts such as NaCl needed for electrolyte balance; essential amino acids such as glutamate needed for protein synthesis; sugars such as glucose needed for energy; and acids such as citric acid that indicate the palatability of various foods (oranges, in the case of citrate). Bitter-tasting molecules, including plant alkaloids like atropine, quinine, and strychnine, indicate foods that may be poisonous. Placing bitter compounds in the mouth usually deters ingestion unless one “acquires a taste” for the substance, as for the quinine in tonic water.

The taste system encodes information about the quantity as well as the identity of stimuli. In general, the higher the stimulus concentration, the greater the perceived intensity of taste. Threshold concentrations for most ingested tastants are quite high, however. For example, the threshold concentration for citric acid is about 2 m*M;* for salt (NaCl), 10 m*M*; and for sucrose, 20 m*M*. (Recall that the perceptual threshold for some odorants is as low as 0.01 n*M*.) Because the body requires substantial concentrations of salts and carbohydrates, taste cells may respond only to relatively high concentrations of these essential substances in order to promote an adequate intake. Clearly, it is advantageous for the taste system to detect potentially dangerous substances (e.g., bitter-tasting plant compounds that may be noxious or poisonous) at much lower concentrations. Thus the threshold concentration for quinine is 0.008 m*M*, and for strychnine 0.0001 m*M*. As in olfaction, gustatory sensitivity declines with age. Adults tend to add more salt and spices to food than children. The decreased sensitivity to salt can be problematic for older people with electrolyte and/or fluid balance problems. Unfortunately, a safe and effective substitute for NaCl has not yet been developed.

There is a common misconception that sweet is perceived at the tip of the tongue, salt along its posterolateral edges, sour along the mediolateral edges, and bitter on the back of the tongue. This arrangement was initially proposed in 1901 by Deiter Hanig, who measured taste thresholds for NaCl, sucrose, quinine, and hydrochloric acid (HCl). Hanig never said that other regions of the tongue were *insensitive* to these chemicals, but only indicated which regions were *most* sensitive. People missing the anterior part of their tongue (or who have facial nerve lesions) can still taste sweet and salty stimuli. In fact, all of these tastes can be detected over the full surface the tongue (Figure 14.14A). However, different regions of the tongue do have different thresholds. Because the tip of the tongue is most responsive to sweet-tasting compounds, and because these compounds produce pleasurable sensations, information from this region activates feeding behaviors such as mouth movements, salivary secretion, insulin release, and swallowing. In contrast, responses to bitter compounds are greatest on the back of the tongue. Activation of this region by bitter-tasting substances elicits protrusion of the tongue and other protective reactions that prevent ingestion. Sour-tasting compounds elicit grimaces, puckering responses, and massive salivary secretion to dilute the tastant.

Based on general agreement across cultures, there are five perceptually distinct categories of taste: salt, sour, sweet, umami (from the Japanese word for delicious, *umami* refers to savory tastes, including monosodium glutamate and other amino acids), and bitter. However, there are obvious limitations to this classification. People experience a variety of taste sensations in addition to these five, including astringent (cranberries and tea), pungent (hot peppers and ginger), fat, starchy, and various metallic tastes, to name only a few. In addition, mixtures of chemicals may elicit entirely new taste sensations. But even though the "taste code" defined by the five primary taste classes is not yet fully understood, these tastes correspond to distinct classes of receptors in subsets of taste cells. Thus, taste perception is closely linked to the molecular biology of taste transduction.

Idiosyncratic Responses to Tastants

Taste responses vary among individuals. For example, many people (about 30–40% of the U.S. population) cannot taste the bitter compound phenylthiocarbamide (PTC) but can taste molecules such as quinine and caffeine that also produce bitter sensations. Indeed, humans can be divided into two groups with quite different thresholds for bitter compounds containing the N—C=S group found in PTC. The difference between these individuals is the presence of a single autosomal gene (*Ptc*) with a dominant (tasters) and

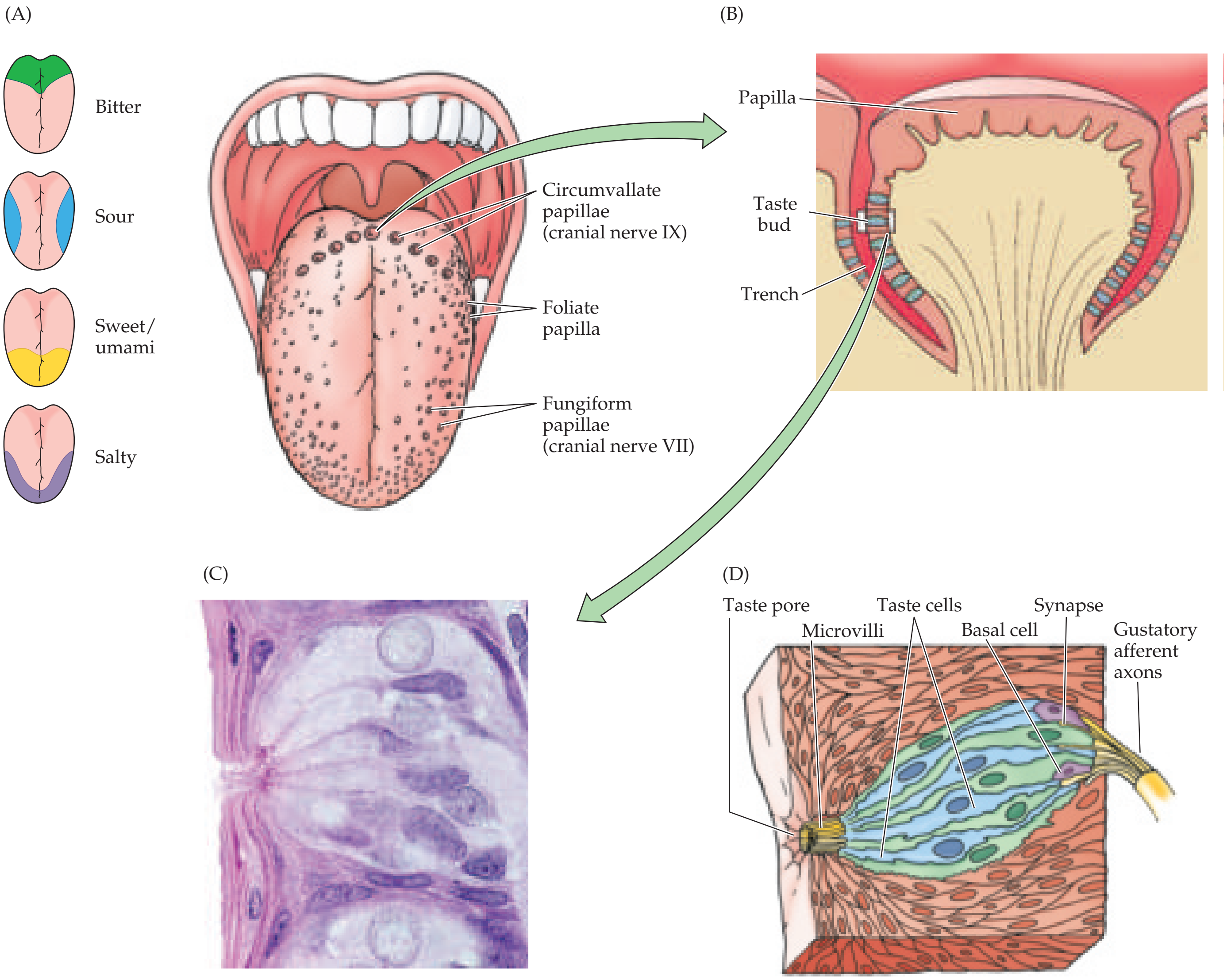

(A)
Bitter
Sour
Sweet/
umami
Salty
Circumvallate
papillae
(cranial nerve IX)
Foliate
papilla
Fungiform
papillae
(cranial nerve VII)
(B)
Papilla
Taste
bud
Trench
(C)
(D)
Taste pore
Microvilli
Taste cells
Basal cell
Synapse
Gustatory
afferent
axons

Figure 14.14 Taste buds and the peripheral innervation of the tongue. (A) Distribution of taste papillae on the dorsal surface of the tongue. Different responses to sweet, salty, sour, and bitter tastants recorded in the three cranial nerves that innervate the tongue and epiglottis are indicated at left. (B) Diagram of a circumvallate papilla showing location of individual taste buds. (C) Light micrograph of a taste bud. (D) Diagram of a taste bud, showing various types of taste cells and the associated gustatory nerves. The apical surface of the receptor cells have microvilli that are oriented toward the taste pore. (C from Ross, Rommell and Kaye, 1995.)

a recessive (non-tasters) allele. Interestingly, people who are extremely sensitive to PTC or its analogues—so-called called "supertasters"—have more taste buds than normal and tend to avoid certain foods such as grapefruit, green tea, and broccoli, all of which contain bitter-tasting compounds. Thus, an individual's genetic makeup with respect to taste receptors has implications for diet, and even health.

The relationship between taste perception and the molecular character of tastants is also variable. A number of quite different compounds taste sweet to humans. These include saccharides (glucose, sucrose, and fructose), organic anions (saccharin), amino acids (aspartame, or Nutrasweet®), L-phenyalanine methyl ester, and proteins (monellin and thaumatin). People can distinguish among different sweeteners, and some find saccharin to have a bitter-tasting component. One reason for such discrimination is that some of these compounds activate separate receptors. For example, saccharides activate cAMP pathways, whereas nonsaccharide sweeteners such as amino acids activate IP_3 pathways. Thus the perceptual experience of "sweet" encompasses much more than the taste of sucrose. It can be elicited by various sensory transduction mechanisms, and may generate sensory qualities different from those generated by sucrose.

Taste sensitivity for salt also relies on a number of mechanisms. Not all salts, or even all monovalent chloride salts, activate the same pathway. Psychophysical studies have shown that amiloride, a diuretic that blocks Na^+ entry through amiloride-sensitive Na^+ channels, decreases the taste intensity of NaCl and LiCl, but not KCl. Although LiCl tastes salty, it cannot be used as a substitute for NaCl because it has profound effects on the central nervous system—clinically, LiCl is used to treat bipolar disorders. Sodium succinate, NH_4Cl, and CsCl do not taste exclusively salty. Indeed, CsCl has a bitter or salty-bitter taste that probably arises from the inhibition of K^+ channels. Additional evidence for a distinct receptor for NaCl comes from developmental studies. Infants up to 4 months old can distinguish between water and sucrose (and lactose), water and acid, and water and bitter tastants, but they cannot distinguish between water and a 0.2 *M* NaCl solution. Thus, either the receptor for Na^+ has not yet been expressed, or, if expressed, it is not yet functional. Infants between the ages of 4 and 6 months, however, can discriminate between NaCl solutions and water, and children can detect the full salty taste of NaCl at about 4 years of age.

Clearly, a given individual's perception of tastants results from many idiosyncracies of the taste system. These idiosyncracies may underlie personal preferences and aversions that lead to individual variation in ingestive behaviors (eating and drinking). The French aphorism *chacun à son goût* ("each to his own taste") reflects not only individual preferences but the biology of the taste-sensing system.

The Organization of the Peripheral Taste System

Approximately 4000 taste buds in humans are distributed throughout the oral cavity and upper alimentary canal. Taste buds are about 50 mm wide at their base and approximately 80 mm long, each containing 30 to 100 taste cells (the sensory receptor cells), plus a few basal cells (Figure 14.14B–D). About 75% percent of all taste buds are found on the dorsal surface of the tongue in small elevations called **papillae** (see Figure 14.14A). There are three types of papillae: **fungiform** (which contain about 25% of the total number of taste buds), **circumvallate** (which contain 50% of the taste buds), and **foliate** (which contain 25%). Fungiform papillae are found only on the anterior two-thirds of the tongue; the highest density (about $30/cm^2$) is at the tip. Fungiform papillae have a mushroom-like structure (hence their name) and typically have about 3 taste buds at their apical surface. There are 9 circumvallate papillae arranged in a chevron at the rear of the tongue. Each consists of a circular trench containing about 250 taste buds along the trench walls. Two foliate papillae are present on the posterolateral tongue, each having about 20 parallel ridges with about 600 taste buds in their walls. Thus, chemical stimuli on the tongue first stimulate receptors in the fungiform papillae and then in the foliate and circumvallate papillae. Tastants subsequently stimulate scattered taste buds in the pharynx, larynx, and upper esophagus.

Taste cells in individual taste buds (see Figure 14.14C,D) synapse with primary afferent axons from branches of three cranial nerves: the facial (VII), glossopharyngeal (IX), and vagus (X) nerves (see Figure 14.13). The taste cells in fungiform papillae on the anterior tongue are innervated exclusively by the chorda tympani branch of the facial nerve; in circumvallate papillae, the taste cells are innervated exclusively by the lingual branch of the glossopharyngeal nerve; and in the palate they are innervated by the greater superior petrosal branch of the facial nerve. Taste buds of the epiglottis and esophagus are innervated by the superior laryngeal branch of the vagus nerve.

The initiating events of chemosensory transduction occur in the taste cells, which have receptors on microvilli that emerge from the apical surface of the taste cell (see Figure 14.14D and 14.15). The apical surfaces of individual taste cells in taste buds are clustered in a small opening (about 1 mm) near the surface of the tongue called a **taste pore**. The synapses that relay the receptor activity are made onto the afferent axons of the various cranial nerves at the basal surface. Like olfactory receptor neurons (and presumably for the same reasons), taste cells have a lifetime of only about 2 weeks and are normally regenerated from basal cells.

Taste Receptors and the Transduction of Taste Signals

The major perceptual categories of taste—salty, sour, sweet, umami, and bitter—are represented by five distinct classes of taste receptors. These receptors are found in the apical microvilli of taste cells. Salty and sour tastes are primarily elicited by ionic stimuli such as the positively charged ions in salts (like Na^+ from NaCl), or the H^+ in acids (acetic acid, for example, which gives vinegar its sour taste). These ions in salty and sour tastants initiate sensory transduction via specific ion channels: the amiloride-sensitive Na^+ channel for salty tastes, and an H^+-sensitive, cation-selective channel for sour (Figures 14.15 and 14.16). The receptor potential generated by the positive inward current carried either by Na^+ for salty or H^+ for sour depolarizes the taste cell. This initial depolarization leads to the activation of voltage-gated Na^+ channels in the basolateral aspect of the taste cell. This additional depolarization activates voltage-gated Ca^{2+} channels, leading to the release of neurotransmitter from the basal aspect of the taste cell and the activation of action potentials in ganglion cell axons (Figure 14.15).

In humans and other mammals, sweet and amino acid (umami) receptors are heteromeric G-protein-coupled receptors that share a common seven-transmembrane receptor subunit called T1R3, which is paired with the T1R2 seven-transmembrane receptor for perception of sweet, or with the T1R1 receptor for amino acids (Figure 14.16). The T1R2 and T1R1 receptors are expressed in different subsets of taste cells, indicating that there are, respectively, sweet- and amino acid-selective cells in the taste buds (see Figure 14.17). Upon binding sugars or other sweet stimuli, the T1R2/T1R3 receptor initiates a G-protein-mediated signal transduction cascade that leads to the activation of the phospholipase C isoform $PLC_{\beta 2}$, leading in turn to increased concentrations of inositol triphosphate (IP_3) and to the opening of TRP channels (specifically the $TRPM_5$ channel), which depolarizes the taste cell via increased intracellular Ca^{2+}. Similarly, the T1R1/T1R3 receptor is broadly tuned to the 20 standard L-amino acids found in proteins (but not to their D-amino acid enantiomers). Transduction of amino acid stimuli via the T1R1/T1R3 receptor also reflects G-protein-coupled intracellular signaling leading to $PLC_{\beta 2}$-mediated activation of the $TRPM_5$ channel and depolarization of the taste cell (see Figure 14.16).

Another family of G-protein-coupled receptors known as the T2R receptors transduce bitter tastes. There are approximately 30 T2R subtypes en-

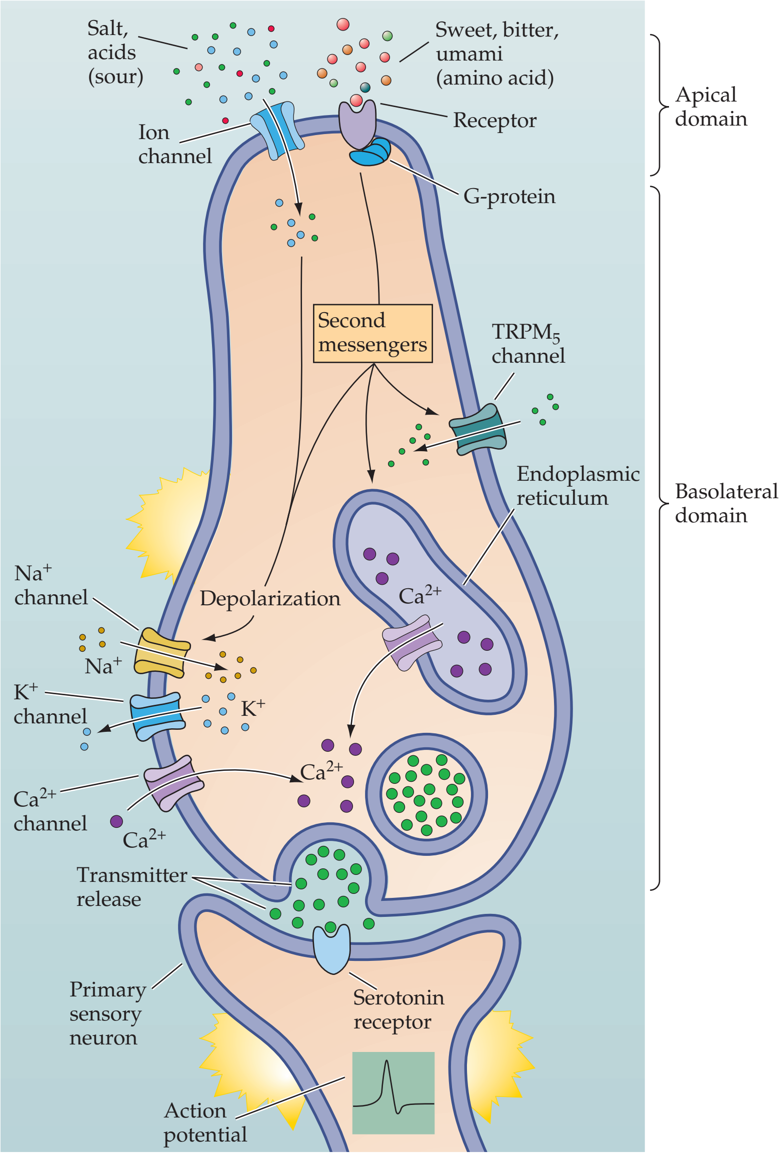

Salt, acids (sour)
Sweet, bitter, umami (amino acid)
Ion channel
Receptor
G-protein
Apical domain
Second messengers
TRPM$_5$ channel
Endoplasmic reticulum
Basolateral domain
Na^+ channel
Depolarization
Ca^{2+}
Na^+
K^+ channel
K^+
Ca^{2+}
Ca^{2+} channel
Ca^{2+}
Transmitter release
Primary sensory neuron
Serotonin receptor
Action potential

Figure 14.15 Basic components of sensory transduction in taste cells. Taste cells are polarized epithelial cells with an apical and a basolateral domain separated by tight junctions. Tastant-transducing channels (salt and sour) and G-protein-coupled receptors (sweet, amino acid, and bitter) are limited to the apical domain. Intracellular signaling components that are coupled to taste receptor molecules (G-proteins and various second messenger-related molecules) are also enriched in the apical domain. Voltage-regulated Na^+, K^+, and Ca^{2+} channels that mediate release of neurotransmitter from presynaptic specializations at the base of the cell onto terminals of peripheral sensory afferents are limited to the basolateral domain, as is endoplasmic reticulum that also modulates intracellular Ca^{2+} concentration and contributes to the release of neurotransmitter. The neurotransmitter serotonin, among others, is found in taste cells, and serotonin receptors are found on the sensory afferents. Finally, the TRPM$_5$ channel, which facilitates G-protein-coupled receptor-mediated depolarization, is expressed in taste cells. Its localization to apical versus basal domains is not yet known.

coded by 30 genes in humans and other mammals, and multiple T2R subtypes are expressed in single taste cells. Nevertheless, T2R receptors are not expressed in the same taste cells as T1R1, 2, and 3 receptors. Thus, the receptor cells for bitter tastants are presumably a distinct class. Although the transduction of bitter stimuli relies on a similar mechanism to that for sweet and amino acid tastes, a taste cell-specific G-protein, **gustducin**, is found primarily in T2R-expressing taste cells and apparently contributes to the transduction of bitter tastes. The remaining steps in bitter transduction are similar to those for sweet and amino acids: PLC$_{\beta 2}$-mediated activation of TRPM$_5$ channels depolarizes the taste cell, resulting in the release of neurotransmitter at the synapse between the taste cell and sensory ganglion cell axon.

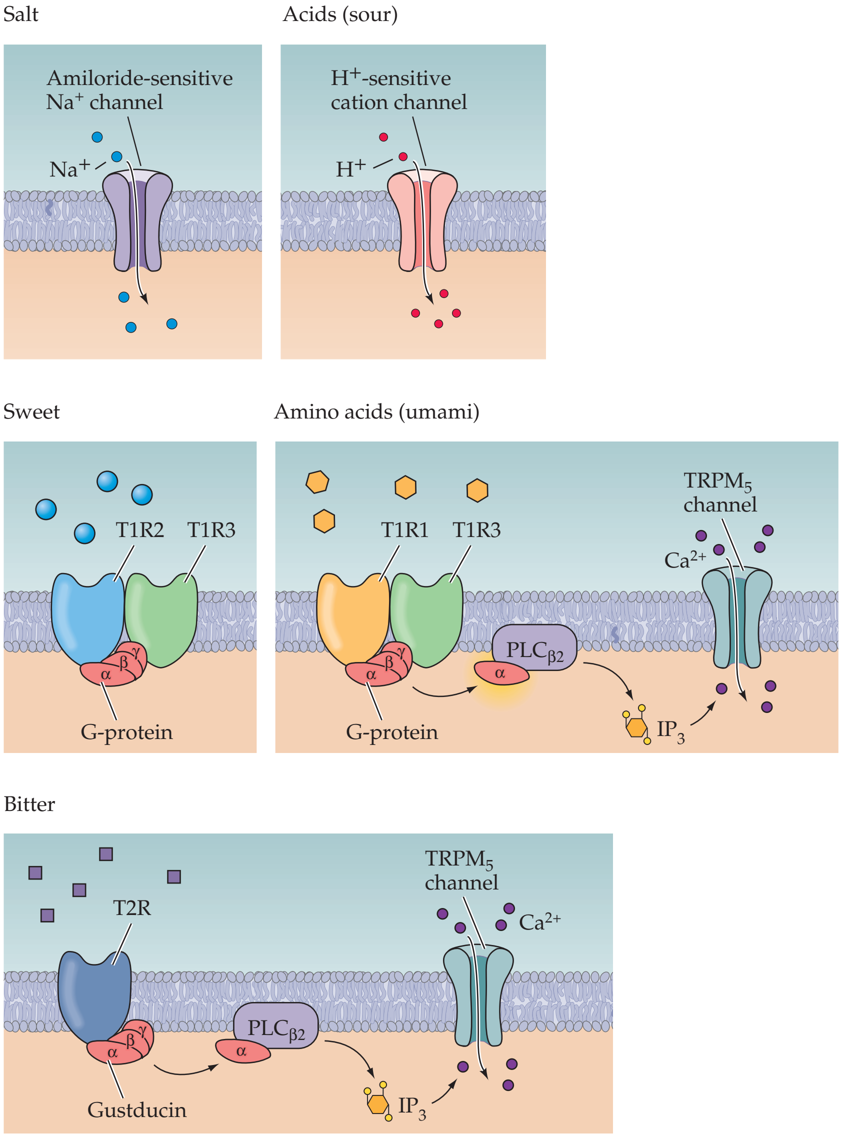


Figure 14.16 Molecular mechanisms of taste transduction via ion channels and G-protein-coupled receptors. Cation selectivity of the amiloride-sensitive Na$^+$ versus the H$^+$-sensitive proton channel provides the basis for specificity of salt and sour tastes. In each case, positive current via the cation channel leads to depolarization of the cell. For sweet, amino acid (umami), and bitter tastants, different classes of G-protein-coupled receptors mediate transduction. For sweet tastants, heteromeric complexes of the T1R2 and T1R3 receptors transduce stimuli via a PLC$_{\beta 2}$-mediated, IP$_3$-dependent mechanism that leads to activation of the TRPM$_5$ Ca^{2+} channel. For amino acids, heteromeric complexes of T1R1 and T1R3 receptors transduce stimuli via the same PLC$_{\beta 2}$/IP$_3$/TRPM$_5$-dependent mechanism. Bitter tastes are transduced via a distinct set of G-protein-coupled receptors, the T2R receptor subtypes.The details of T2R receptors are less well established; however, they apparently associate with the taste cell-specific G-protein gustducin, which is not found in sweet or amino acid receptor-expressing taste cells. Nevertheless, stimulus-coupled depolarization for bitter tastes relies upon the same PLC$_{\beta 2}$/IP$_3$/TRPM$_5$-dependent mechanism used for sweet and amino acid taste transduction.

Neural Coding in the Taste System

In the taste system, **neural coding** refers to the way that the identity, concentration, and "hedonic" (pleasurable or aversive) value of tastants is represented in the pattern of action potentials relayed to the brain. Neurons in the taste system (or in any other sensory system) might be specifically "tuned" to respond with a maximal change in electrical activity to a single taste stimulus. Such tuning is thought to rely on specificity at the level of the receptor cells, as well as on the maintenance of separate channels for the relay of this information from the periphery to the brain. This sort of coding scheme is referred to as a **labeled line code**, since responses in specific cells presumably correspond to distinct stimuli. The segregated expression of sweet, amino acid, and bitter receptors in different taste cells (Figure 14.17) is consistent with labeled line coding.

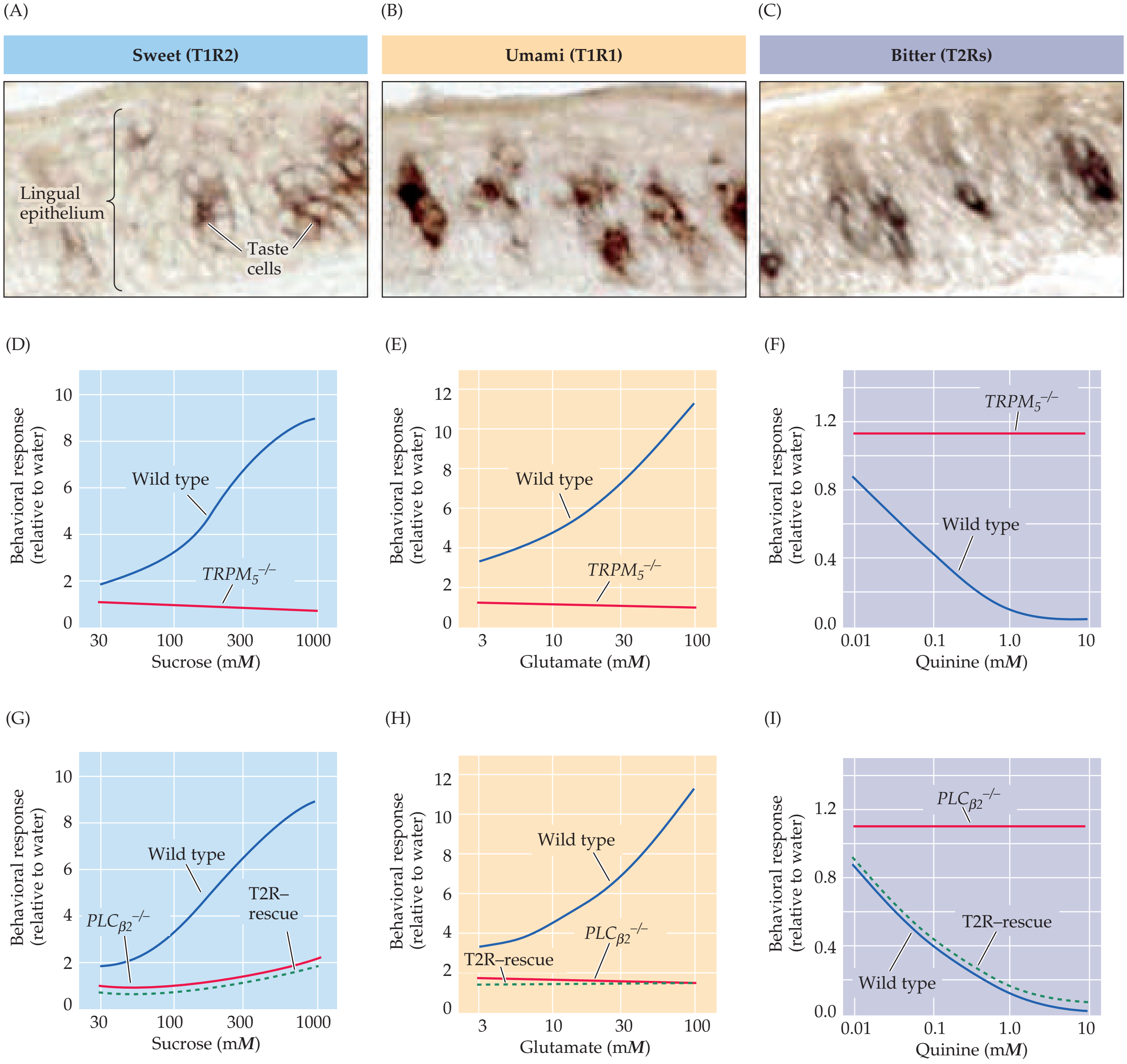
The results of molecular genetic experiments in mice are consistent with a labeled line code. Initial support came from studies in which the genes that specify the sweet and amino acid heteromeric receptors (T1R2 and T1R1) were inactivated in mice. Such mice lack behavioral responses to a broad range of sweet or amino acid stimuli, depending on the gene that has been inactivated. Moreover, recordings of electrical activity in the relevant branches of cranial nerves VII, IX, or X showed that action potentials in response to sweet or amino acid stimuli were lost in parallel with the genetic mutation and behavioral change. Finally, these deficits in transduction and perception were unchanged at a broad range of concentrations, indicating that the molecular specificity of each receptor is quite rigid—the remaining receptors could not respond, even at high concentrations of sweet or amino acid stimuli.

These observations suggest that sweet and amino acid transduction and perception depend on labeled lines from the periphery. Bitter taste proved harder to analyze because of the larger number of T2R bitter receptors. To circumvent this challenge, Charles Zuker, Nicholas Ryba and colleagues took advantage of the shared aspects of intracellular signaling for sweet, amino acid, and bitter tastes (see Figure 14.16). Thus, if the genes for either the $TRPM_5$ channel or $PLC_{\beta2}$ are inactivated, behavioral and physiological responses to sweet, amino acid, and bitter stimuli are abolished while salty and sour perception (and the related physiological responses) remain (Figure 14.17). To evaluate whether taste cells expressing the T2R family of receptors provide a labeled line for bitter tastes, $PLC_{\beta2}$ was selectively re-expressed in T2R-expressing taste cells in a *$PLC_{\beta2}$* mutant mouse. Thus, in these mice, only the taste cells that normally express the T2R subset of taste cells (which expresses most of the T2R receptors in concert) can now tranduce taste signals. If these cells provide a labeled line for bitter tastes, the "rescued" mice (i.e., those expressing $PLC_{\beta2}$ in T2R cells) should regain their perceptual and physiological responses to bitter taste, but not to sweet or amino acid tastes. This was indeed the result of the experiment—behavioral and physiological responses to bitter tastes, but not sweet or amino acid tastes, were restored to normal levels (see Figure 14.17). Evidently, taste coding for sweet, amino acid, and bitter—as judged by taste perception and the related neural activity in peripheral nerves—reflects labeled lines established by the identity of the taste receptor proteins and the subsets of taste cells that express them.

These observations support the labeled line hypothesis for primary tastes; however, they do not provide a full account of how either primary or complex tastes are represented in patterns of neural activity in central stations of the taste system (e.g., the solitary nucleus, the thalamus, or the insular cortex). Indeed, little is known about the representation of taste information in the CNS, either at the level of recordings from individual cells or the representation of tastes across an ensemble of neurons in relevant areas of the brainstem, thalamus, or cortex.

Trigeminal Chemoreception

The third of the major chemosensory systems, the trigeminal chemosensory system, consists of polymodal nociceptive neurons and their axons in the trigeminal nerve (cranial nerve V) and, to a lesser degree, nociceptive neurons whose axons run in the glossopharyngeal and vagus nerves (IX and X) (see Appendix A). These neurons and their associated endings are typically



activated by chemicals classified as irritants, including air pollutants (e.g., sulfur dioxide), ammonia (smelling salts), ethanol (liquor), acetic acid (vinegar), carbon dioxide (in soft drinks), menthol (in various inhalants sensation; see Box A in Chapter 9), and capsaicin (the compound in hot chili peppers that elicits the characteristic burning sensation). Irritant-sensitive polymodal nociceptors alert the organism to potentially harmful chemical stimuli that have been ingested, respired, or come in contact with the face, and are closely tied to the trigeminal pain system discussed in Chapter 9.

Trigeminal chemosensory information from the face, scalp, cornea, and mucous membranes of the oral and nasal cavities is relayed via the three major sensory branches of the trigeminal nerve: the ophthalmic, maxillary,

◀ **Figure 14.17** Specificity in peripheral taste coding supports the labeled line hypothesis. (A–C) Sweet (A), amino acid (B), and bitter (C) receptors are expressed in different subsets of taste cells. (D–E) The gene for the $TRPM_5$ channel can be inactivated, or "knocked out," in mice ($TRPM_5^{-/-}$) and behavioral responses measured with a taste preference test. The mouse is presented with two drinking spouts, one with water and the other with a tastant; behavioral responses are measured as the frequency of licking of the two spouts. For pleasant tastes like sweet (sucrose; D) or umami (glutamate; E) control mice lick the spout with the tastant more frequently, and higher concentrations of tastant leads to increased response (blue lines). In $TRPM_5^{-/-}$ mice, this behavioral response (i.e., a preference for the tastant versus water) is eliminated at all concentrations (red lines). (F) For an aversive tastant like bitter quinine, control mice prefer water. This behavioral response—which is initially low—is further diminished with higher quinine concentrations (blue line). Inactivation of $TRPM_5$ also eliminates this behavioral response, regardless of tastant concentration (red line). (G–I) When the $PLC_{\beta 2}$ gene is knocked out, behavioral response to (G) sucrose, (H) glutamate, and (I) quinine are eliminated (red lines). When $PLC_{\beta 2}$ is re-expressed only in T2R-expressing taste cells, behavioral responses to sucrose and glutamate are not rescued (dotted green lines in G and H); however, the behavioral response to quinine is restored to normal levels (compare the blue and dotted green lines in I). (After Zhang et al., 2003.)

and mandibular (Figure 14.18). The central target of these afferent axons is the spinal component of the trigeminal nucleus, which relays this information to the ventral posterior medial nucleus of the thalamus and thence to the somatic sensory cortex and other cortical areas that process facial irritation and pain (see Chapter 9).

Many compounds classified as irritants can also be recognized as odors or tastes; however, the threshold concentrations for trigeminal chemoreception are much higher than those for olfaction or taste. When potentially irritating compounds are presented to people who have lost their sense of smell, perceptual thresholds are found to be approximately 100 times higher than those of normal subjects who perceive the compounds as odors (Figure 14.19). Similar differences occur in identifying chemicals as tastes rather than irritants. Thus, 0.1 *M* NaCl has a salty taste, but 1.0 *M* NaCl is perceived as an irritant. Another common irritant is ethanol. When placed on the tongue at moderate temperatures and high concentrations—as in drinking vodka "neat"—ethanol produces a burning sensation.

A variety of physiological responses mediated by the trigeminal chemosensory system are triggered by exposure to irritants. These include increased salivation, vasodilation, tearing, nasal secretion, sweating, decreased respiratory rate, and bronchoconstriction. Consider, for instance, the experience that follows the ingestion of capsaicin (see Box A in Chapter 9). These reactions are generally protective in that they dilute the stimulus (tearing, salivation, sweating) and prevent inhaling or ingesting more of it.

The receptors for irritants are primarily on the terminal branches of polymodal nociceptive neurons, as described for the pain and temperature systems in Chapter 9. Although these receptors respond to many of the same stimuli as olfactory receptor neurons (e.g., aldehydes, alcohols), they are probably not activated by the same mechanism; for instance, the G-protein-coupled receptors for odorants are found only in olfactory receptor neurons. With the exception of capsaicin and acidic stimuli, both of which activate cation-selective ion channels, little is known about the transduction mechanisms for irritants, or their central processing.

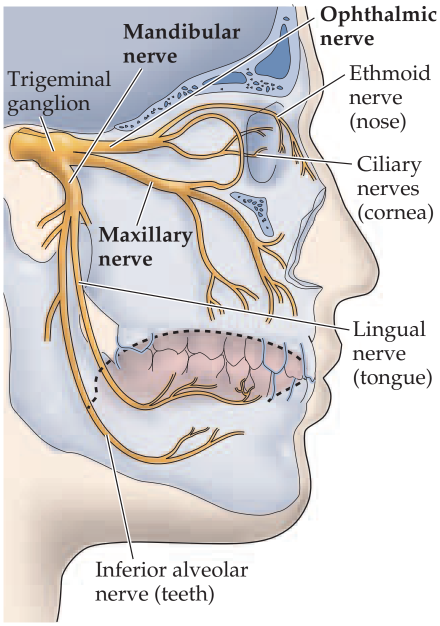


Figure 14.18 Diagram of the branches of the trigeminal nerve that innervate the oral, nasal, and ocular cavities. The chemosensitive structures innervated by each trigeminal branch are indicated in parentheses.

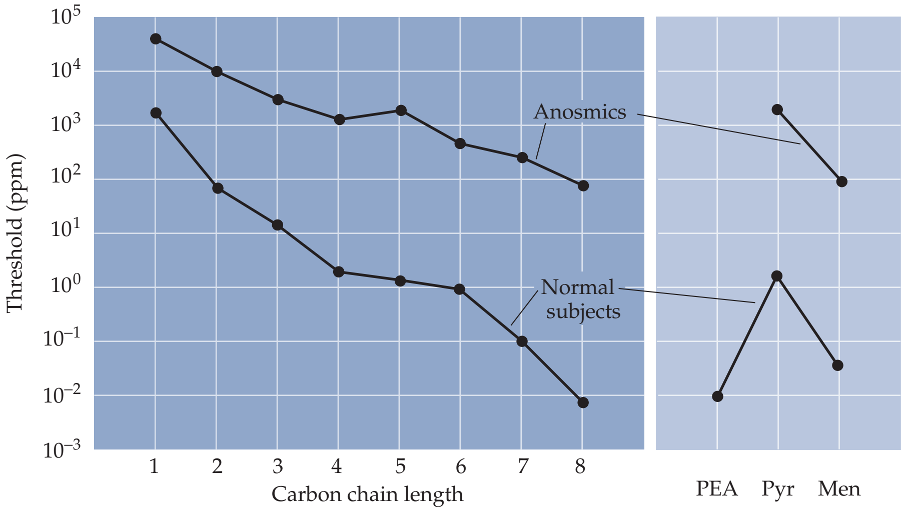


Figure 14.19 Perceptual thresholds in anosmic and normal subjects for related organic chemicals. In anosmics, these chemicals are only detected as irritants at relatively high concentrations (indicated here in parts per million, ppm); in normal subjects, they are first detected at much lower concentrations as odors. The numbers 1–8 stand for the aliphatic alcohols from methanol to 1-octanol. Perceptual thresholds for three additional common irritants—phenylethyl alcohol (PEA), pyridine (Pyr), and menthol (Men)—are shown at the far right. (After Commetto-Muniz and Cain, 1990.)

Summary

The chemical senses—olfaction, taste, and the trigeminal chemosensory system—all contribute to sensing airborne or soluble molecules from a variety of sources. Humans and other mammals rely on this information for behaviors as diverse as attraction, avoidance, reproduction, feeding, and avoiding potentially dangerous circumstances. Receptor neurons in the olfactory epithelium transduce chemical stimuli into neuronal activity via the stimulation of G-protein-linked receptors; this interaction leads to elevated levels of second messengers such as cAMP, which in turn open cation-selective channels. These events generate receptor potentials in the membrane of the olfactory receptor neuron, and ultimately action potentials in the afferent axons of these cells. Taste receptor cells, in contrast, use a variety of mechanisms for transducing chemical stimuli. These include ion channels that are directly activated by salts and amino acids, and G-protein-linked receptors that activate second messengers. For both smell and taste, the spatial and temporal patterns of action potentials provide information about the identity and intensity of chemical stimuli. The trigeminal chemosensory system responds to irritants by means of mechanisms that are less well understood. Each of the approximately 10,000 odors that humans recognize (and an undetermined number of tastes and irritant molecules) is evidently encoded by the activity of a distinct population of receptor cells in the nose, tongue, and oral cavity. Olfaction, taste, and trigeminal chemosensation all are relayed via specific pathways in the central nervous system. Receptor neurons in the olfactory system project directly to the olfactory bulb. In the taste system, information is relayed centrally by cranial sensory ganglion cells to the solitary nucleus in the brainstem. In the trigeminal chemosensory system, information is relayed via trigeminal ganglion cell projections to the spinal trigeminal nucleus in the brainstem. Each of these structures project in turn to many sites in the brain that process chemosensory information in ways that give rise to some of the most sublime pleasures that humans experience.

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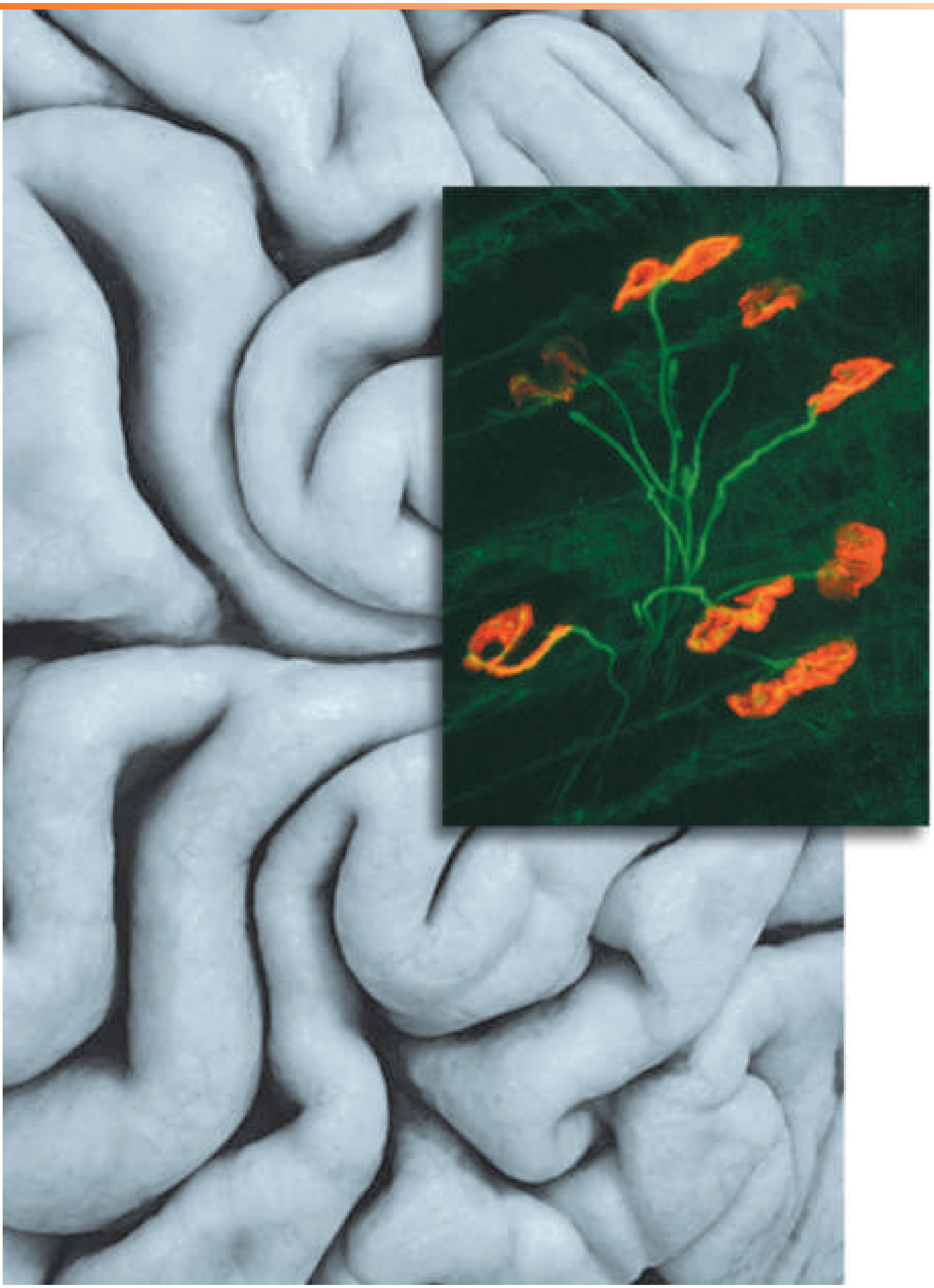
Movement and Its Central Control

III



Fluorescence photomicrograph showing motor axons (green) and neuromuscular synapses (orange) in transgenic mice that have been genetically engineered to express fluorescent proteins. (Courtesy of Bill Snider and Jeff Lichtman.)

UNIT III

Movement and Its Central Control

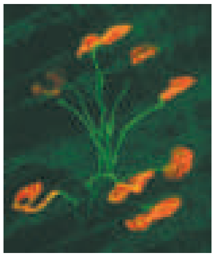
15 Lower Motor Neuron Circuits and Motor Control
16 Upper Motor Neuron Control of the Brainstem and Spinal Cord
17 Modulation of Movement by the Basal Ganglia
18 Modulation of Movement by the Cerebellum
19 Eye Movements and Sensory Motor Integration
20 The Visceral Motor System

Movements, whether voluntary or involuntary, are produced by spatial and temporal patterns of muscular contractions orchestrated by the brain and spinal cord. Analysis of these circuits is fundamental to an understanding of both normal behavior and the etiology of a variety of neurological disorders. This unit considers the brainstem and spinal cord circuitry that make elementary reflex movements possible, as well as the circuits that organize the intricate patterns of neural activity responsible for more complex motor acts. Ultimately, all movements produced by the skeletal musculature are initiated by "lower" motor neurons in the spinal cord and brainstem that directly innervate skeletal muscles; the innervation of visceral smooth muscles is separately organized by the autonomic divisions of the visceral motor system.

The lower motor neurons are controlled directly by local circuits within the spinal cord and brainstem that coordinate individual muscle groups, and indirectly by "upper" motor neurons in higher centers that regulate those local circuits, thus enabling and coordinating complex sequences of movements. Especially important are circuits in the basal ganglia and cerebellum that regulate the upper motor neurons, ensuring that movements are performed with spatial and temporal precision.

Specific disorders of movement often signify damage to a particular brain region. For example, clinically important and intensively studied neurodegenerative disorders such as Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis result from pathological changes in different parts of the motor system. Knowledge of the various levels of motor control is essential for understanding, diagnosing, and treating these diseases.

Chapter 15



Lower Motor Neuron Circuits and Motor Control

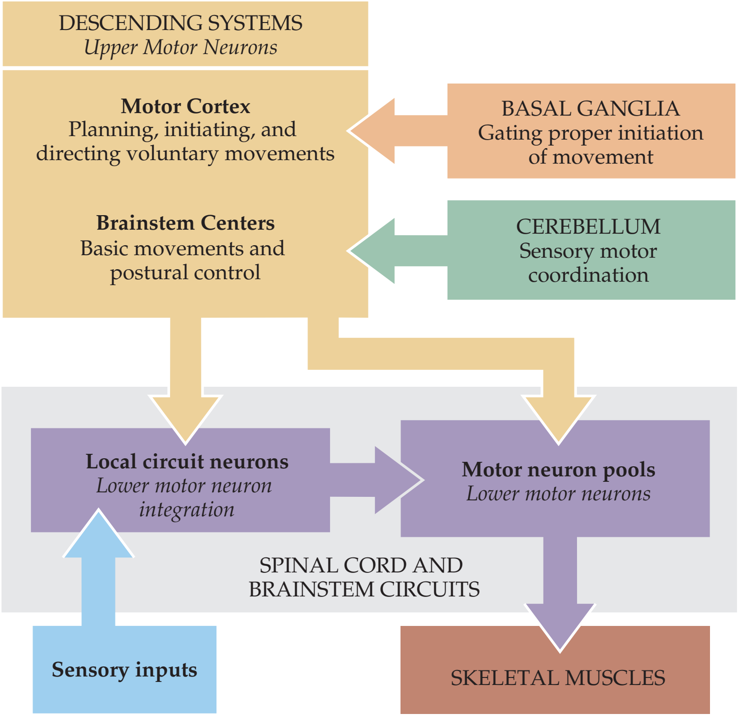
Overview

Skeletal (striated) muscle contraction is initiated by "lower" motor neurons in the spinal cord and brainstem. The cell bodies of the lower neurons are located in the ventral horn of the spinal cord gray matter and in the motor nuclei of the cranial nerves in the brainstem. These neurons (also called α motor neurons) send axons directly to skeletal muscles via the ventral roots and spinal peripheral nerves, or via cranial nerves in the case of the brainstem nuclei. The spatial and temporal patterns of activation of lower motor neurons are determined primarily by local circuits located within the spinal cord and brainstem. Descending pathways from higher centers comprise the axons of "upper" motor neurons and modulate the activity of lower motor neurons by influencing this local circuitry. The cell bodies of upper motor neurons are located either in the cortex or in brainstem centers, such as the vestibular nucleus, the superior colliculus, and the reticular formation. The axons of the upper motor neurons typically contact the local circuit neurons in the brainstem and spinal cord, which, via relatively short axons, contact in turn the appropriate combinations of lower motor neurons. The local circuit neurons also receive direct input from sensory neurons, thus mediating important sensory motor reflexes that operate at the level of the brainstem and spinal cord. Lower motor neurons, therefore, are the final common pathway for transmitting neural information from a variety of sources to the skeletal muscles.

Neural Centers Responsible for Movement

The neural circuits responsible for the control of movement can be divided into four distinct but highly interactive subsystems, each of which makes a unique contribution to motor control (Figure 15.1). The first of these subsystems is the local circuitry within the gray matter of the spinal cord and the analogous circuitry in the brainstem. The relevant cells include the **lower motor neurons** (which send their axons out of the brainstem and spinal cord to innervate the skeletal muscles of the head and body, respectively) and the **local circuit neurons** (which are the major source of synaptic input to the lower motor neurons). All commands for movement, whether reflexive or voluntary, are ultimately conveyed to the muscles by the activity of the lower motor neurons; thus these neurons comprise, in the words of the great British neurophysiologist Charles Sherrington, the "final common path" for movement. The local circuit neurons receive sensory inputs as well as descending projections from higher centers. Thus, the circuits they form provide much of the coordination between different muscle groups that is

Figure 15.1 Overall organization of neural structures involved in the control of movement. Four systems—local spinal cord and brainstem circuits, descending modulatory pathways, the cerebellum, and the basal ganglia—make essential and distinct contributions to motor control.


DESCENDING SYSTEMS
Upper Motor Neurons
Motor Cortex
Planning, initiating, and directing voluntary movements
Brainstem Centers
Basic movements and postural control
BASAL GANGLIA
Gating proper initiation of movement
CEREBELLUM
Sensory motor coordination
Local circuit neurons
Lower motor neuron integration
Motor neuron pools
Lower motor neurons
SPINAL CORD AND BRAINSTEM CIRCUITS
Sensory inputs
SKELETAL MUSCLES

essential for organized movement. Even after the spinal cord is disconnected from the brain in an experimental animal such as a cat, appropriate stimulation of local spinal circuits elicits involuntary but highly coordinated limb movements that resemble walking.

The second motor subsystem consists of the **upper motor neurons** whose cell bodies lie in the brainstem or cerebral cortex and whose axons descend to synapse with the local circuit neurons or, more rarely, with the lower motor neurons directly. The upper motor neuron pathways that arise in the cortex are essential for the initiation of voluntary movements and for complex spatiotemporal sequences of skilled movements. In particular, descending projections from cortical areas in the frontal lobe, including Brodmann's area 4 (the **primary motor cortex**), the lateral part of area 6 (the **lateral premotor cortex**), and the medial part of area 6 (the **medial premotor cortex**) are essential for planning, initiating, and directing sequences of voluntary movements. Upper motor neurons originating in the brainstem are responsible for regulating muscle tone and for orienting the eyes, head, and body with respect to vestibular, somatic, auditory, and visual sensory information. Their contributions are thus critical for basic navigational movements, and for the control of posture.

The third and fourth subsystems are complex circuits with output pathways that have no direct access to either the local circuit neurons or the lower motor neurons; instead, they control movement by regulating the activity of the upper motor neurons. The third and larger of these subsystems, the **cerebellum**, is located on the dorsal surface of the pons (see Chapter 1). The cerebellum acts via its efferent pathways to the upper motor neurons as a servomechanism, detecting the difference, or "motor error," between an intended movement and the movement actually performed (see Chapter 19). The cerebellum uses this information about discrepancies to mediate both real-time and long-term reductions in these motor errors (the latter being a form of motor learning). As might be expected from this account, patients with cerebellar damage exhibit persistent errors in movement. The fourth subsystem, embedded in the depths of the forebrain, consists of a group of structures collectively referred to as the **basal ganglia** (see Chapter 1). The basal ganglia suppress unwanted movements and prepare (or "prime") upper motor neuron circuits for the initiation of movements. The problems associated with disorders of basal ganglia, such as Parkinson's disease and Huntington's disease, attest to the importance of this complex in the initiation of voluntary movements (see Chapter 17).

Despite much effort, the sequence of events that leads from volitional thought to movement is still poorly understood. The picture is clearest, however, at the level of control of the muscles themselves. It therefore makes sense to begin an account of motor behavior by considering the anatomical and physiological relationships between lower motor neurons and the muscle fibers they innervate.

Motor Neuron–Muscle Relationships

By injecting individual muscle groups with visible tracers that are transported by the axons of the lower motor neurons back to their cell bodies, the lower motor neurons that innervate each of the body's skeletal muscles can be seen in histological sections of the ventral horns of the spinal cord. Each lower motor neuron innervates muscle fibers within a single muscle, and all the motor neurons innervating a single muscle (called the **motor neuron pool** for that muscle) are grouped together into rod-shaped clusters that run parallel to the long axis of the cord for one or more spinal cord segments (Figure 15.2).

An orderly relationship between the location of the motor neuron pools and the muscles they innervate is evident both along the length of the spinal cord and across the mediolateral dimension of the cord, an arrangement that in effect provides a spatial map of the body's musculature. For example, the motor neuron pools that innervate the arm are located in the cervical enlargement of the cord and those that innervate the leg in the lumbar enlargement (see Chapter 1). The mapping, or topography, of motor neuron pools in the mediolateral dimension can be appreciated in a cross section through the cervical enlargement (the level illustrated in Figure 15.3). Thus, neurons that innervate the axial musculature (i.e., the postural muscles of the trunk) are located medially in the cord. Lateral to these cell groups are motor neuron pools innervating muscles located progressively more laterally in the body. Neurons that innervate the muscles of the shoulders (or pelvis, if one were to look at a similar section in the lumbar enlargement; see Figure 15.2) are the next most lateral group, whereas those that innervate the proximal muscles of the arm (or leg) are located laterally to these. The motor neuron pools that innervate the distal parts of the extremities, the fingers or toes, lie farthest from the midline. This spatial organization provides clues about the functions of the descending upper motor neuron pathways described in the following chapter; some of these pathways terminate primarily in the medial region of the spinal cord, which is concerned with postural muscles, whereas other pathways terminate more laterally, where they have access to the lower motor neurons that control movements of the distal parts of the limbs, such as, the toes and the fingers.

Two types of lower motor neuron are found in these neuronal pools. Small **γ motor neurons** innervate specialized muscle fibers that, in combina-

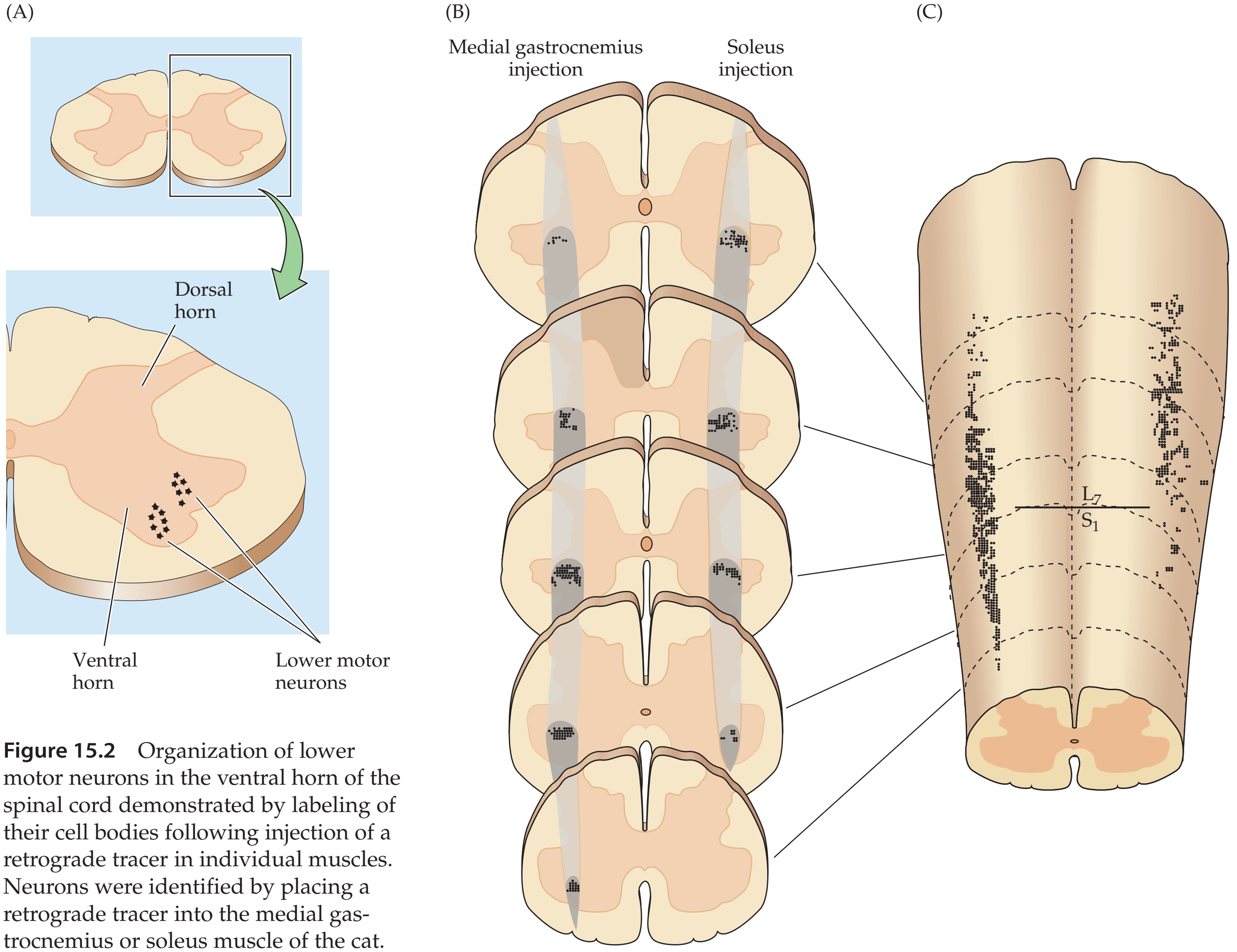


Figure 15.2 Organization of lower motor neurons in the ventral horn of the spinal cord demonstrated by labeling of their cell bodies following injection of a retrograde tracer in individual muscles. Neurons were identified by placing a retrograde tracer into the medial gastrocnemius or soleus muscle of the cat. (A) Section through the lumbar level of the spinal cord showing the distribution of labeled cell bodies. Lower motor neurons form distinct clusters (motor pools) in the ventral horn. Spinal cord cross sections (B) and a reconstruction seen from the dorsal surface (C) illustrate the distribution of motor neurons innervating individual skeletal muscles in both axes of the cord. The cylindrical shape and distinct distribution of different pools are especially evident in the dorsal view of the reconstructed cord. The dashed lines in (C) represent individual lumbar and sacral spinal cord segments. (After Burke et al., 1977.)

tion with the nerve fibers that innervate them, are actually sensory receptors called muscle spindles (see Chapter 8). The muscle spindles are embedded within connective tissue capsules in the muscle, and are thus referred to as intrafusal muscle fibers (*fusal* means capsular). The intrafusal muscle fibers are also innervated by sensory axons that send information to the brain and spinal cord about the length and tension of the muscle. The function of the γ motor neurons is to regulate this sensory input by setting the intrafusal muscle fibers to an appropriate length (see the next section). The second type of lower motor neuron, called **α motor neurons**, innervates the extrafusal muscle fibers, which are the striated muscle fibers that actually generate the forces needed for posture and movement.

Although the following discussion focuses on the lower motor neurons in the spinal cord, comparable sets of motor neurons responsible for the control of muscles in the head and neck are located in the brainstem. The latter neurons are distributed in the eight motor nuclei of the cranial nerves in the medulla, pons, and midbrain (see Appendix A). Somewhat confusingly, but quite appropriately, these motor neurons in the brainstem are also called lower motor neurons.

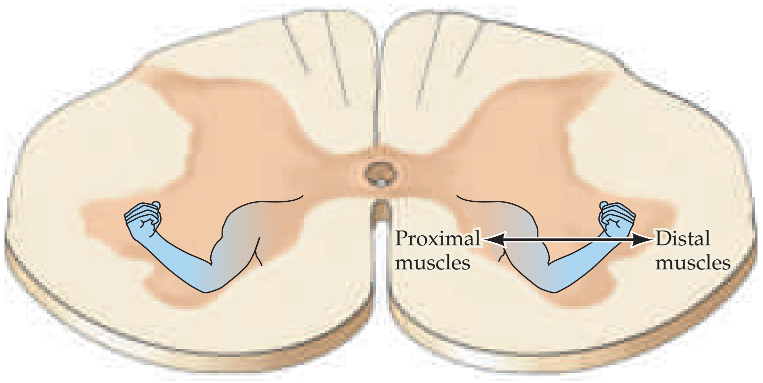


Figure 15.3 Somatotopic organization of lower motor neurons in a cross section of the ventral horn at the cervical level of the spinal cord. Motor neurons innervating axial musculature are located medially, whereas those innervating the distal musculature are located more laterally.

The Motor Unit

Most mature extrafusal skeletal muscle fibers in mammals are innervated by only a single α motor neuron. Since there are by far more muscle fibers than motor neurons, individual motor axons branch within muscles to synapse on many different fibers that are typically distributed over a relatively wide area within the muscle, presumably to ensure that the contractile force of the motor unit is spread evenly (Figure 15.4). In addition, this arrangement reduces the chance that damage to one or a few α motor neurons will significantly alter a muscle's action. Because an action potential generated by a

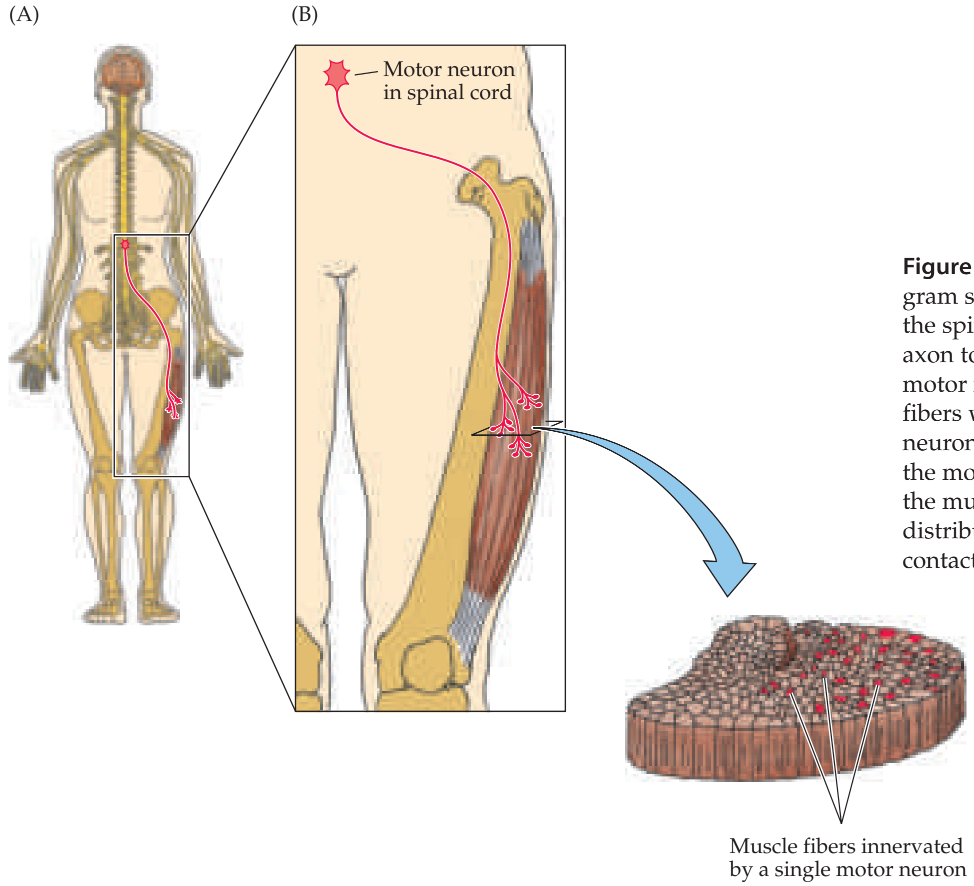

(A)
(B)
Motor neuron in spinal cord
Muscle fibers innervated by a single motor neuron

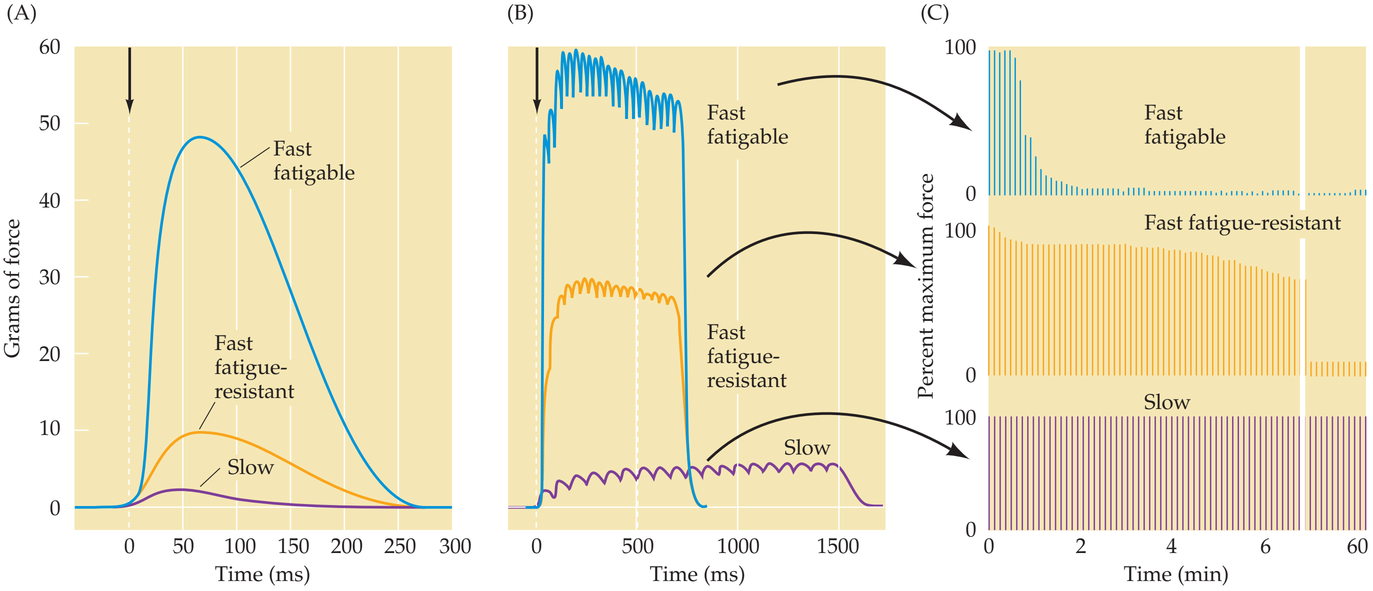
Figure 15.4 The motor unit. (A) Diagram showing a lower motor neuron in the spinal cord and the course of its axon to its target muscle. (B) Each motor neuron synapses with multiple fibers within the muscle. The motor neuron and the fibers it contacts define the motor unit. Cross section through the muscle shows the relatively diffuse distribution of muscle fibers (red dots) contacted by the motor neuron.

motor neuron normally brings to threshold all of the muscle fibers it contacts, a single α motor neuron and its associated muscle fibers together constitute the smallest unit of force that can be activated to produce movement. Sherrington was again the first to recognize this fundamental relationship between an α motor neuron and the muscle fibers it innervates, for which he coined the term **motor unit**.

Both motor units and the α motor neurons themselves vary in size. Small α motor neurons innervate relatively few muscle fibers and form motor units that generate small forces, whereas large motor neurons innervate larger, more powerful motor units. Motor units also differ in the types of muscle fibers that they innervate. In most skeletal muscles, the smaller motor units comprise small "red" muscle fibers that contract slowly and generate relatively small forces; but, because of their rich myoglobin content, plentiful mitochondria, and rich capillary beds, such small red fibers are resistant to fatigue (these units are also innervated by relatively small α motor neurons). These small units are called **slow (S) motor units** and are especially important for activities that require sustained muscular contraction, such as the maintenance of an upright posture. Larger α motor neurons innervate larger, pale muscle fibers that generate more force; however, these fibers have sparse mitochondria and are therefore easily fatigued. These units are called **fast fatigable (FF) motor units** and are especially important for brief exertions that require large forces, such as running or jumping. A third class of motor units has properties that lie between those of the other two. These **fast fatigue-resistant (FR) motor units** are of intermediate size and are not quite as fast as FF units. They generate about twice the force of a slow motor unit and, as the name implies, are substantially more resistant to fatigue (Figure 15.5).

These distinctions among different types of motor units indicate how the nervous system produces movements appropriate for different circumstances. In most muscles, small, slow motor units have lower thresholds for activation than the larger units and are tonically active during motor acts that require sustained effort (standing, for instance). The thresholds for the large, fast motor units are reached only when rapid movements requiring great force are made, such as jumping. The functional distinctions between

Figure 15.5 Comparison of the force and fatigability of the three different types of motor units. In each case, the response reflects stimulation of a single motor neuron. (A) Change in muscle tension in response to a single motor neuron action potential. (B) Tension in response to repetitive stimulation of the motor neurons. (C) Response to repeated stimulation at a level that evokes maximum tension. The ordinate represents the force generated by each stimulus. Note the strikingly different fatigue rates. (After Burke et al., 1974.)



the various classes of motor units also explain some structural differences among muscle groups. For example, a motor unit in the soleus (a muscle important for posture that comprises mostly small, slow units) has an average innervation ratio of 180 muscle fibers for each motor neuron. In contrast, the gastrocnemius, a muscle that comprises both small and larger units, has an innervation ratio of ~1000–2000 muscle fibers per motor neuron, and can generate forces needed for sudden changes in body position. More subtle variations are present in athletes on different training regimens. Thus, muscle biopsies show that sprinters have a larger proportion of powerful but rapidly fatiguing pale fibers in their leg muscles than do marathoners. Other differences are related to the highly specialized functions of particular muscles. For instance, the eyes require rapid, precise movements but little strength; in consequence, extraocular muscle motor units are extremely small (with an average innervation ratio of only 3!) and have a very high proportion of muscle fibers capable of contracting with maximal velocity.

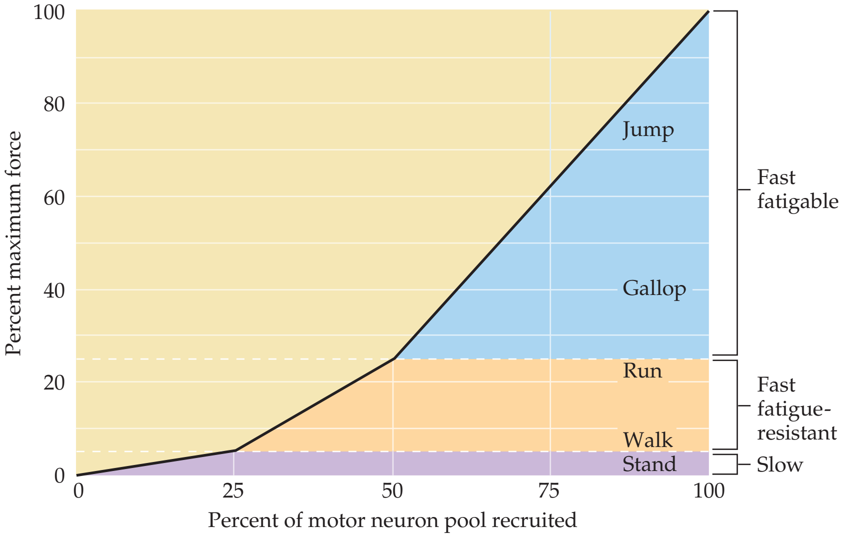
The Regulation of Muscle Force

Increasing or decreasing the number of motor units active at any one time changes the amount of force produced by a muscle. In the 1960s, Elwood Henneman and his colleagues at Harvard Medical School found that progressive increases in muscle tension could be produced by progressively increasing the activity of axons that provide input to the relevant pool of lower motor neurons. This gradual increase in tension results from the recruitment of motor units in a fixed order according to their size. By stimulating either sensory nerves or upper motor pathways that project to a lower motor neuron pool while measuring the tension changes in the muscle, Henneman found that in experimental animals only the smallest motor units in the pool are activated by weak synaptic stimulation. When synaptic input increases, progressively larger motor units that generate larger forces are recruited: As the synaptic activity driving a motor neuron pool increases, low threshold S units are recruited first, then FR units, and finally, at the highest levels of activity, the FF units. Since these original experiments, evidence for the orderly recruitment of motor units has been found in a variety of voluntary and reflexive movements. As a result, this systematic relationship has come to be known as the **size principle**.

An illustration of how the size principle operates for the motor units of the medial gastrocnemius muscle in the cat is shown in Figure 15.6. When the animal is standing quietly, the force measured directly from the muscle tendon is only a small fraction (about 5%) of the total force that the muscle can generate. The force is provided by the S motor units, which make up about 25% of the motor units in this muscle. When the cat begins to walk, larger forces are necessary: locomotor activities that range from slow walking to fast running require up to 25% of the muscle's total force capacity. This additional need is met by the recruitment of FR units. Only movements such as galloping and jumping, which are performed infrequently and for short periods, require the full power of the muscle; such demands are met by the recruitment of the FF units. Thus, the size principle provides a simple solution to the problem of grading muscle force: The combination of motor units activated by such orderly recruitment optimally matches the physiological properties of different motor unit types with the range of forces required to perform different motor tasks.

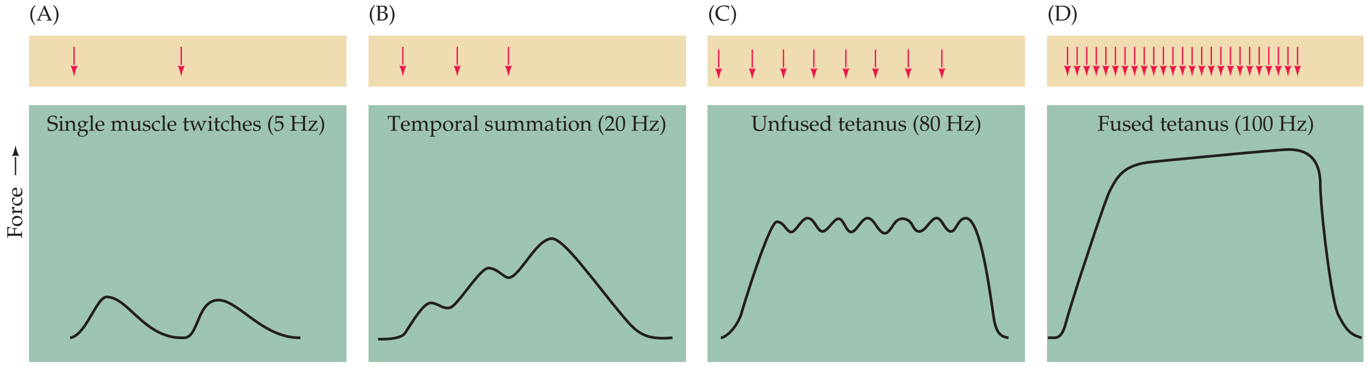
The frequency of the action potentials generated by motor neurons also contributes to the regulation of muscle tension. The increase in force that

Figure 15.6 The recruitment of motor neurons in the cat medial gastrocnemius muscle under different behavioral conditions. Slow (S) motor units provide the tension required for standing. Fast fatigue-resistant (FR) units provide the additional force needed for walking and running. Fast fatigable (FF) units are recruited for the most strenuous activities, such as jumping. (After Walmsley et al., 1978.)



occurs with increased firing rate reflects the summation of successive muscle contractions: The muscle fibers are activated by the next action potential before they have had time to completely relax, and the forces generated by the temporally overlapping contractions are summed (Figure 15.7). The lowest firing rates during a voluntary movement are on the order of 8 per second (Figure 15.8). As the firing rate of individual units rises to a maximum of about 20–25 per second in the muscle being studied here, the amount of force produced increases. At the highest firing rates, individual muscle fibers are in a state of "fused tetanus"—that is, the tension produced in individual motor units no longer has peaks and troughs that correspond to the individual twitches evoked by the motor neuron's action potentials. Under normal conditions, the maximum firing rate of motor neurons is less than that required for fused tetanus (see Figure 15.8). However, the asynchronous firing of different lower motor neurons provides a steady level of input to the muscle, which causes the contraction of a relatively constant number of motor units and averages out the changes in tension due to contractions and relaxations of individual motor units. All this allows the resulting movements to be executed smoothly.

Figure 15.7 The effect of stimulation rate on muscle tension. (A) At low frequencies of stimulation, each action potential in the motor neuron results in a single twitch of the related muscle fibers. (B) At higher frequencies, the twitches sum to produce a force greater than that produced by single twitches. (C) At a still higher frequency of stimulation, the force produced is greater, but individual twitches are still apparent. This response is referred to as unfused tetanus. (D) At the highest rates of motor neuron activation, individual twitches are no longer apparent (a condition called fused tetanus).



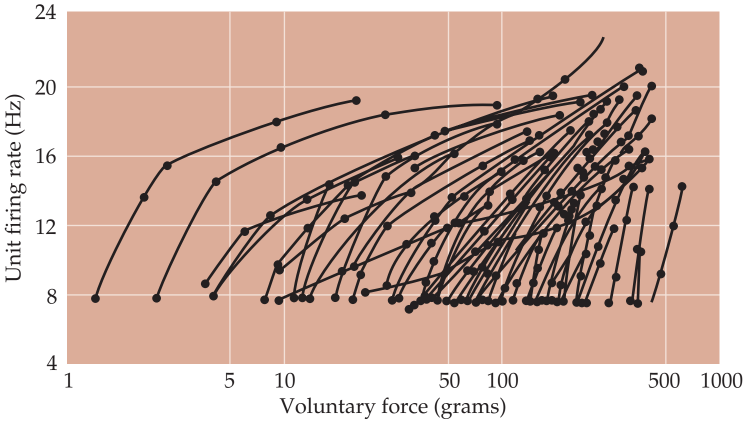
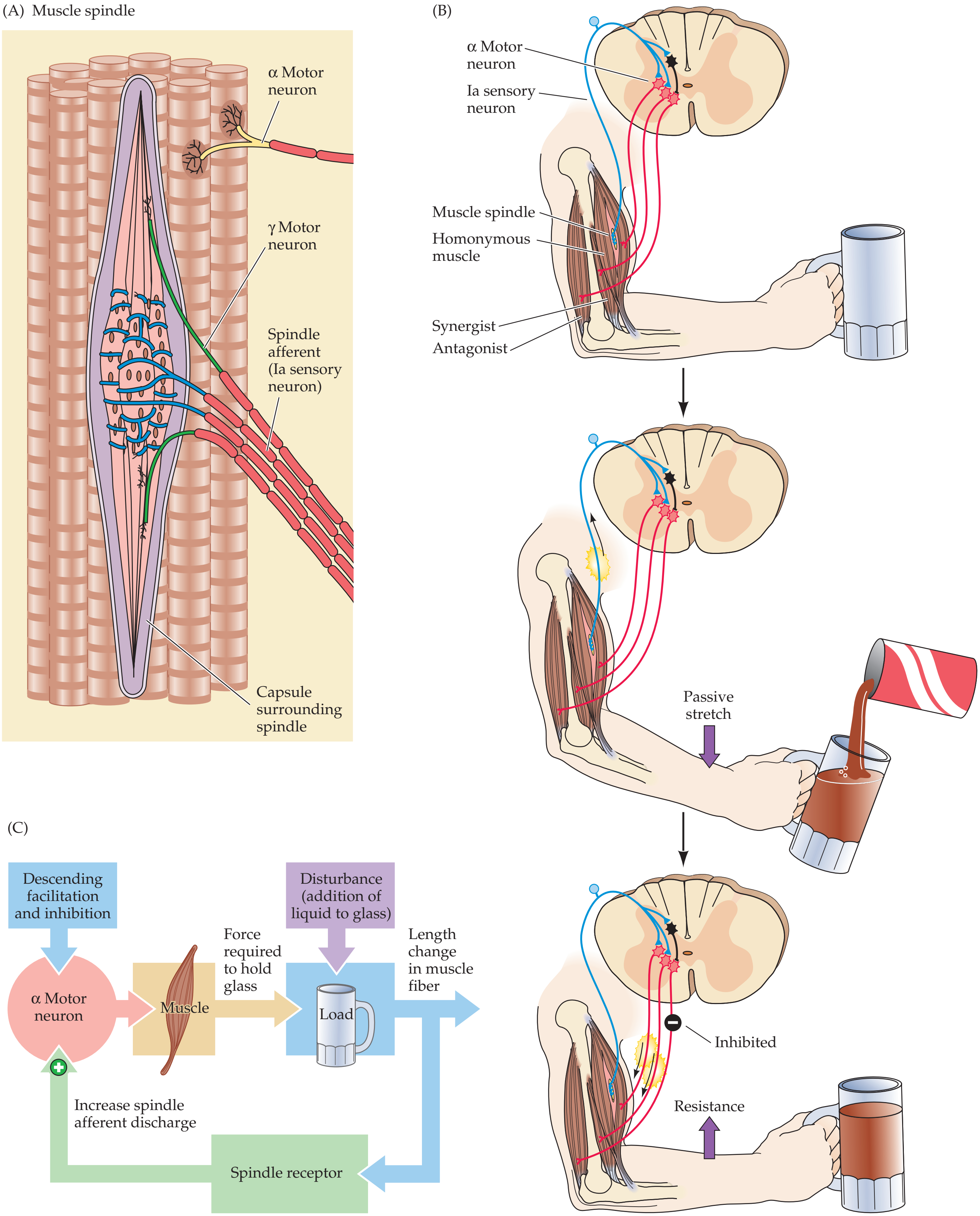


Figure 15.8 Motor units recorded transcutaneously in a muscle of the human hand as the amount of voluntary force produced is progressively increased. Motor units (represented by the lines between the dots) are initially recruited at a low frequency of firing (8 Hz); the rate of firing for each unit increases as the subject generates more and more force. (After Monster and Chan, 1977.)

The Spinal Cord Circuitry Underlying Muscle Stretch Reflexes

The local circuitry within the spinal cord mediates a number of sensory motor reflex actions. The simplest of these reflex arcs entails a sensory response to muscle stretch, which provides direct excitatory feedback to the motor neurons innervating the muscle that has been stretched (Figure 15.9). As already mentioned, the sensory signal for the **stretch reflex** originates in **muscle spindles**, the sensory receptors embedded within most muscles (see the previous section and Chapter 8). The spindles comprise 8–10 intrafusal fibers arranged in parallel with the extrafusal fibers that make up the bulk of the muscle (Figure 15.9A). Large-diameter sensory fibers, called Ia afferents, are coiled around the central part of the spindle. These afferents are the largest axons in peripheral nerves and, since action potential conduction velocity is a direct function of axon diameter (see Chapters 2 and 3), they mediate very rapid reflex adjustments when the muscle is stretched. The stretch imposed on the muscle deforms the intrafusal muscle fibers, which in turn initiate action potentials by activating mechanically gated ion channels in the afferent axons coiled around the spindle. The centrally projecting branch of the sensory neuron forms monosynaptic excitatory connections with the α motor neurons in the ventral horn of the spinal cord that innervate the same (homonymous) muscle and, via local circuit neurons, forms inhibitory connections with the α motor neurons of antagonistic (heteronymous) muscles. This arrangement is an example of what is called *reciprocal innervation* and results in rapid contraction of the stretched muscle and simultaneous relaxation of the antagonist muscle. All of this leads to especially rapid and efficient responses to changes in the length or tension in the muscle (Figure 15.9B). The excitatory pathway from a spindle to the α motor neurons innervating the same muscle is unusual in that it is a monosynaptic reflex; in most cases, sensory neurons from the periphery do not contact the lower motor neuron directly but exert their effects through local circuit neurons.

This monosynaptic reflex arc is variously referred to as the “stretch,” “deep tendon,” or “myotatic” reflex, and it is the basis of the knee, ankle, jaw, biceps, or triceps responses tested in a routine neurological examination. The tap of the reflex hammer on the tendon stretches the muscle and therefore excites an afferent volley of activity in the Ia sensory axons that innervate the muscle spindles. The afferent volley is relayed to the α motor neurons in the brainstem or spinal cord, and an efferent volley returns to the muscle (see Figure 1.5). Since muscles are always under some degree of


(A) Muscle spindle
α Motor neuron
γ Motor neuron
Spindle afferent (Ia sensory neuron)
Capsule surrounding spindle
(B)
α Motor neuron
Ia sensory neuron
Muscle spindle
Homonymous muscle
Synergist
Antagonist
Passive stretch
Inhibited
Resistance
(C)
Descending facilitation and inhibition
Disturbance (addition of liquid to glass)
α Motor neuron
Muscle
Force required to hold glass
Load
Length change in muscle fiber
Increase spindle afferent discharge
Spindle receptor

◀ **Figure 15.9** Stretch reflex circuitry. (A) Diagram of muscle spindle, the sensory receptor that initiates the stretch reflex. (B) Stretching a muscle spindle leads to increased activity in Ia afferents and an increase in the activity of α motor neurons that innervate the same muscle. Ia afferents also excite the motor neurons that innervate synergistic muscles, and inhibit the motor neurons that innervate antagonists (see also Figure 1.5). (C) The stretch reflex operates as a negative feedback loop to regulate muscle length.

stretch, this reflex circuit is normally responsible for the steady level of tension in muscles called **muscle tone**. Changes in muscle tone occur in a variety of pathological conditions, and it is these changes that are assessed by examination of tendon reflexes.

In terms of engineering principles, the stretch reflex arc is a negative feedback loop used to maintain muscle length at a desired value (Figure 15.9C). The appropriate muscle length is specified by the activity of descending upper motor neuron pathways that influence the motor neuron pool. Deviations from the desired length are detected by the muscle spindles, since increases or decreases in the stretch of the intrafusal fibers alter the level of activity in the sensory axons that innervate the spindles. These changes lead in turn to adjustments in the activity of the α motor neurons, returning the muscle to the desired length by contracting the stretched muscle and relaxing the opposed muscle group, and by restoring the level of spindle activity to what it was before.

The smaller γ motor neurons control the functional characteristics of the muscle spindles by modulating their level of excitability. As was described earlier, when the muscle is stretched, the spindle is also stretched and the rate of discharge in the afferent fibers increased. When the muscle shortens, however, the spindle is relieved of tension, or “unloaded,” and the sensory axons that innervate the spindle might therefore be expected to fall silent during contraction. However, they remain active. The γ motor neurons terminate on the contractile poles of the intrafusal fibers, and the activation of these neurons causes intrafusal fiber contraction—in this way maintaining the tension on the middle (or equatorial region) of the intrafusal fibers where the sensory axons terminate. Thus, co-activation of the α and γ motor neurons allows spindles to function (i.e., send information centrally) at all muscle lengths during movements and postural adjustments.

The Influence of Sensory Activity on Motor Behavior

The level of γ motor neuron activity often is referred to as γ bias, or gain, and can be adjusted by upper motor neuron pathways as well as by local reflex circuitry. The larger the gain of the stretch reflex, the greater the change in muscle force that results from a given amount of stretch applied to the intrafusal fibers. If the gain of the reflex is high, then a small amount of stretch applied to the intrafusal fibers will produce a large increase in the number of α motor neurons recruited and a large increase in their firing rates; this in turn leads to a large increase in the amount of tension produced by the extrafusal fibers. If the gain is low, a greater stretch is required to generate the same amount of tension in the extrafusal muscle fibers. In fact, the gain of the stretch reflex is continuously adjusted to meet different functional requirements. For example, while standing in a moving bus, the gain of the stretch reflex can be modulated by upper motor neuron pathways to com-

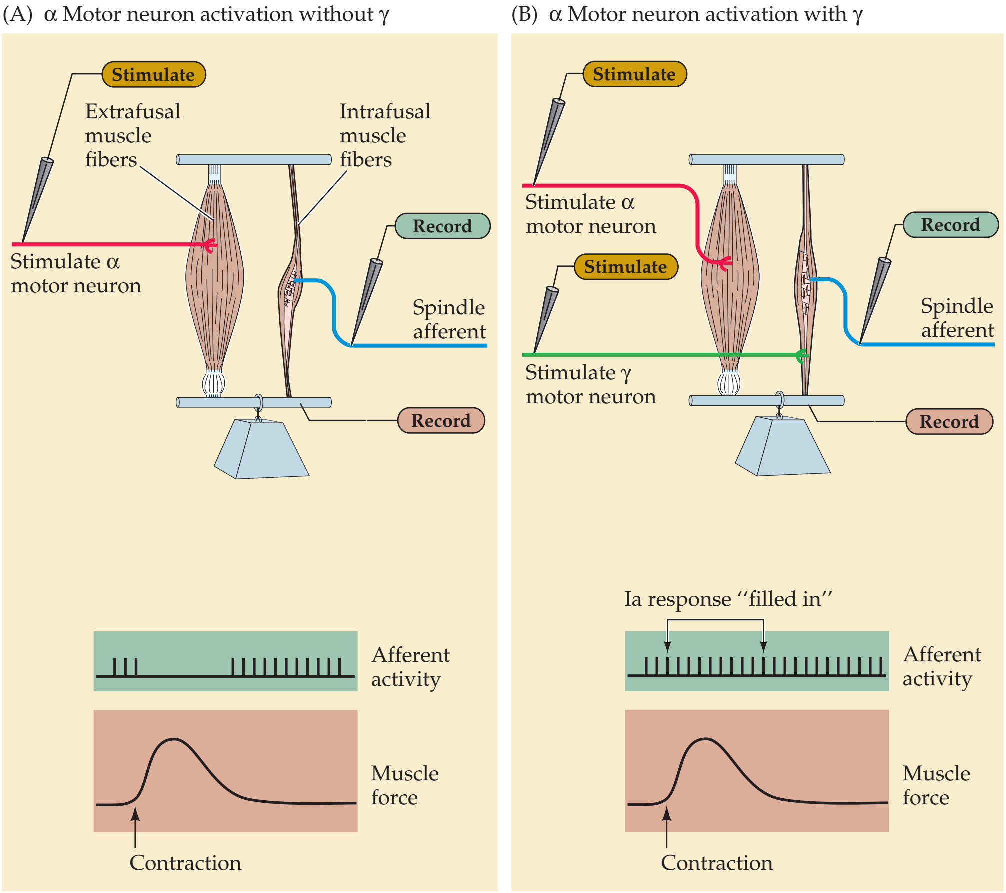

(A) α Motor neuron activation without γ
Stimulate
Extrafusal muscle fibers
Intrafusal muscle fibers
Record
Stimulate α motor neuron
Spindle afferent
Record
Afferent activity
Muscle force
Contraction
(B) α Motor neuron activation with γ
Stimulate
Stimulate α motor neuron
Record
Stimulate
Spindle afferent
Stimulate γ motor neuron
Record
Ia response "filled in"
Afferent activity
Muscle force
Contraction

Figure 15.10 The role of γ motor neuron activity in regulating the responses of muscle spindles. (A) When α motor neurons are stimulated without activation of γ motor neurons, the response of the Ia fiber decreases as the muscle contracts. (B) When both α and γ motor neurons are activated, there is no decrease in Ia firing during muscle shortening. Thus, the γ motor neurons can regulate the gain of muscle spindles so they can operate efficiently at any length of the parent muscle. (After Hunt and Kuffler, 1951.)

pensate for the variable changes that occur as the bus stops and starts or progresses relatively smoothly. During voluntary movements, α and γ motor neurons are often co-activated by higher centers to prevent muscle spindles from being unloaded (Figure 15.10).

In addition, the level of γ motor neuron activity can be modulated independently of α activity if the context of a movement requires it. In general, the baseline activity level of γ motor neurons is high if a movement is relatively difficult and demands rapid and precise execution. For example, recordings from cat hindlimb muscles show that γ activity is high when the animal has to perform a difficult movement such as walking across a narrow beam. Unpredictable conditions, as when the animal is picked up or handled, also lead to marked increases in γ activity and greatly increased spindle responsiveness.

Gamma motor neuron activity, however, is not the only factor that sets the gain of the stretch reflex. The gain also depends on the level of excitability of the α motor neurons that serve as the efferent side of this reflex loop. Thus, in addition to the influence of descending upper motor neuron projections, other local circuits in the spinal cord can change the gain of the stretch reflex by excitation or inhibition of either α or γ motor neurons.

Other Sensory Feedback That Affects Motor Performance

Another sensory receptor that is important in the reflex regulation of motor unit activity is the **Golgi tendon organ**. Golgi tendon organs are encapsulated afferent nerve endings located at the junction of a muscle and tendon (Figure 15.11A; see also Table 9.1). Each tendon organ is innervated by a single group Ib sensory axon (the Ib axons are slightly smaller than the Ia axons that innervate the muscle spindles). In contrast to the parallel arrangement of extrafusal muscle fibers and spindles, Golgi tendon organs are in series with the extrafusal muscle fibers. When a muscle is passively stretched, most of the change in length occurs in the muscle fibers, since they are more elas-

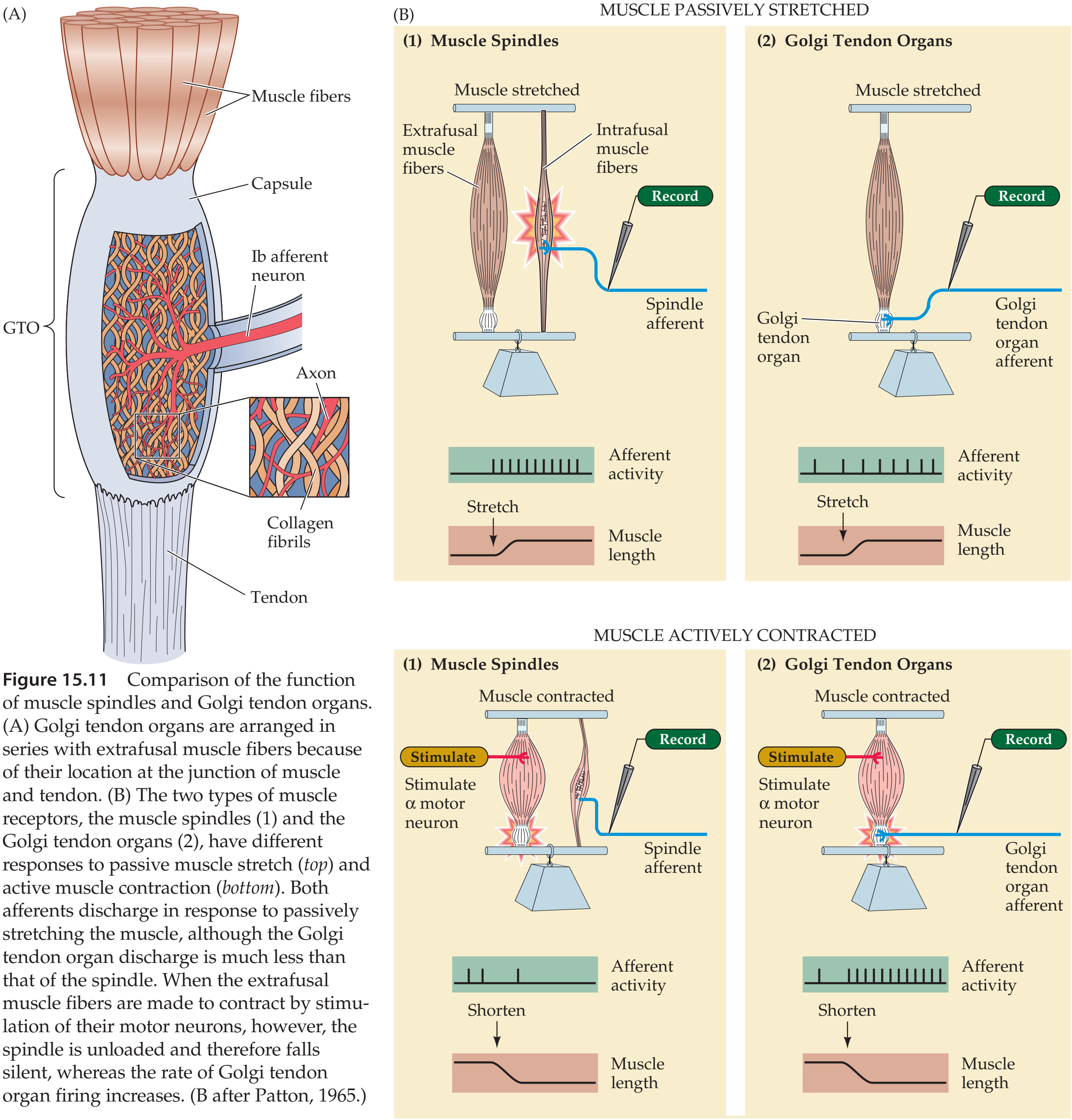

(A)
Muscle fibers
Capsule
Ib afferent neuron
GTO
Axon
Collagen fibrils
Tendon
(B)
MUSCLE PASSIVELY STRETCHED
(1) Muscle Spindles
Muscle stretched
Extrafusal muscle fibers
Intrafusal muscle fibers
Record
Spindle afferent
Afferent activity
Stretch
Muscle length
(2) Golgi Tendon Organs
Muscle stretched
Record
Golgi tendon organ
Golgi tendon organ afferent
Afferent activity
Stretch
Muscle length
MUSCLE ACTIVELY CONTRACTED
(1) Muscle Spindles
Muscle contracted
Stimulate
Stimulate α motor neuron
Record
Spindle afferent
Afferent activity
Shorten
Muscle length
(2) Golgi Tendon Organs
Muscle contracted
Stimulate
Stimulate α motor neuron
Record
Golgi tendon organ afferent
Afferent activity
Shorten
Muscle length

Figure 15.11 Comparison of the function of muscle spindles and Golgi tendon organs. (A) Golgi tendon organs are arranged in series with extrafusal muscle fibers because of their location at the junction of muscle and tendon. (B) The two types of muscle receptors, the muscle spindles (1) and the Golgi tendon organs (2), have different responses to passive muscle stretch (*top*) and active muscle contraction (*bottom*). Both afferents discharge in response to passively stretching the muscle, although the Golgi tendon organ discharge is much less than that of the spindle. When the extrafusal muscle fibers are made to contract by stimulation of their motor neurons, however, the spindle is unloaded and therefore falls silent, whereas the rate of Golgi tendon organ firing increases. (B after Patton, 1965.)

Box A

Locomotion in the Leech and the Lamprey

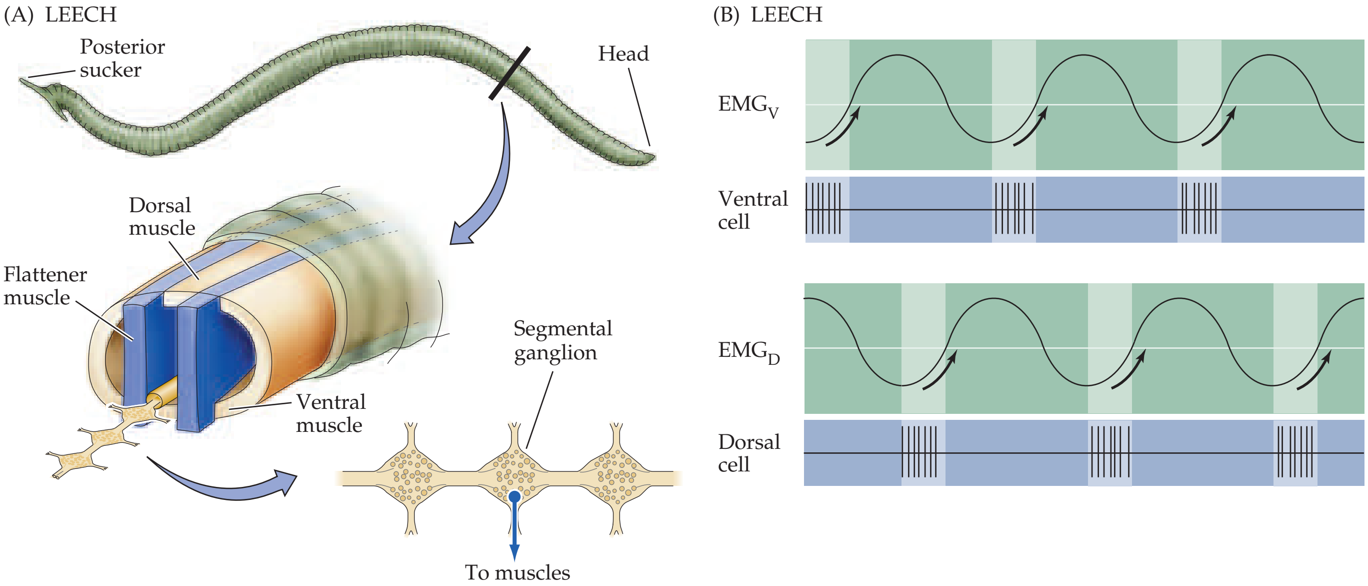
All animals must coordinate body movements so they can navigate successfully in their environment. All vertebrates, including mammals, use local circuits in the spinal cord (central pattern generators) to control the coordinated movements associated with locomotion. The cellular basis of organized locomotor activity, however, has been most thoroughly studied in an invertebrate, the leech, and a simple vertebrate, the lamprey.

Both the leech and the lamprey lack peripheral appendages for locomotion possessed by many vertebrates (limbs, flippers, fins, or their equivalent). Furthermore, their bodies comprise repeating muscle segments (as well as repeating skeletal elements in the lamprey). Thus, in order to move through the water, both animals must coordinate the movement of each segment. They do this by orchestrating a sinusoidal displacement of each body segment in sequence, so that the animal is propelled forward through the water.

The leech is particularly well-suited for studying the circuit basis of coordinated movement. The nervous system in the leech consists of a series of interconnected segmental ganglia, each with motor neurons that innervate the corresponding segmental muscles (Figure A). These segmental ganglia facilitate electrophysiological studies, because there is a limited number of neurons in each and each neuron has a distinct identity. The neurons can thus be recognized and studied from animal to animal, and their electrical activity correlated with the sinusoidal swimming movements.

A central pattern generator circuit coordinates this undulating motion. In the leech, the relevant neural circuit is an ensemble of sensory neurons, interneurons, and motor neurons repeated in each segmental ganglion that controls the local sequence of contraction and relaxation in each segment of the body wall musculature (Figure B). The sensory neurons detect the stretching and contraction of the body wall associated with the sequential swimming movements. Dorsal and ventral motor neurons in the circuit provide innervation to dorsal and ventral muscles, whose phasic contractions propel the leech forward. Sensory information and motor neuron signals are coordinated by interneurons that fire rhythmically, setting up phasic patterns of activity in the dorsal and ventral cells that lead to sinusoidal movement. The intrinsic swimming rhythm is established by a variety of membrane conductances that mediate periodic bursts of suprathreshold action potentials followed by well-defined periods of hyperpolarization.

The lamprey, one of the simplest vertebrates, is distinguished by its clearly



(A) The leech propels itself through the water by sequential contraction and relaxation of the body wall musculature of each segment. The segmental ganglia in the ventral midline coordinate swimming, each ganglion containing a population of identified neurons. (B) Electrical recordings from the ventral (EMG_V) and dorsal (EMG_D) muscles in the leech and the corresponding motor neurons show a reciprocal pattern of excitation for the dorsal and ventral muscles of a given segment.

segmented musculature and by its lack of bilateral fins or other appendages. In order to move through the water, the lamprey contracts and relaxes each muscle segment in sequence (Figure C), which produces a sinusoidal motion, much like that of the leech. Again, a central pattern generator coordinates this sinusoidal movement.

Unlike the leech with its segmental ganglia, the lamprey has a continuous spinal cord that innervates its muscle segments. The lamprey spinal cord is simpler than that of other vertebrates, and several classes of identified neurons occupy stereotyped positions. This orderly arrangement again facilitates the identification and analysis of neurons that constitute the central pattern generator circuit.

In the lamprey spinal cord, the intrinsic firing pattern of a set of interconnected sensory neurons, interneurons and motor neurons establishes the pattern of undulating muscle contractions that underlie swimming (Figure D). The patterns of connectivity between neurons, the neurotransmitters used by each class of cell, and the physiological properties of the elements in the lamprey pattern generator are now known. Different neurons in the circuit fire with distinct rhythmicity, thus controlling specific aspects of the swim cycle (Figure E). Particularly important are reciprocal inhibitory connections across the midline that coordinate the pattern generating circuitry on each side of the spinal cord. This circuitry in the lamprey thus provides a basis for understanding the circuits that control locomotion in more complex vertebrates.

These observations on pattern generating circuits for locomotion in relatively simple animals have stimulated parallel studies of terrestrial mammals in which central pattern generators in the spinal cord also coordinate locomotion. Although different in detail, terrestrial locomotion ultimately relies on the sequential movements similar to those that propel the leech and the lamprey through aquatic environments, and intrinsic physiological properties of spinal cord neurons that establish rythmicity for coordinated movement.

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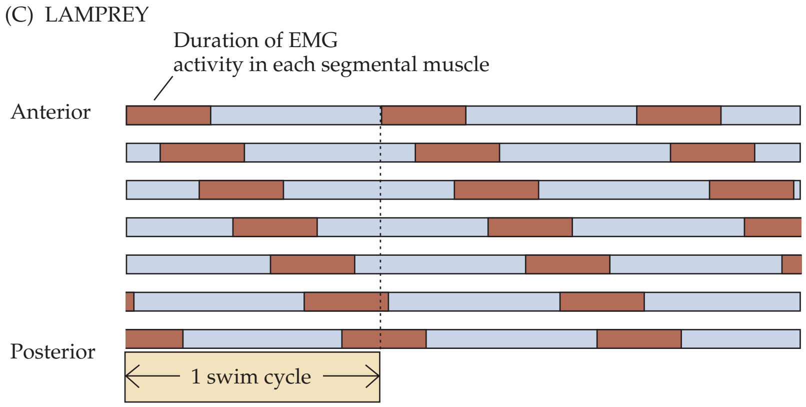
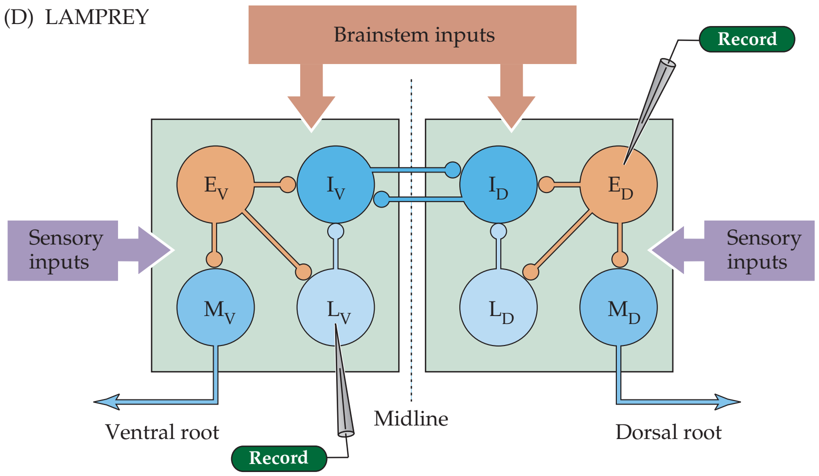
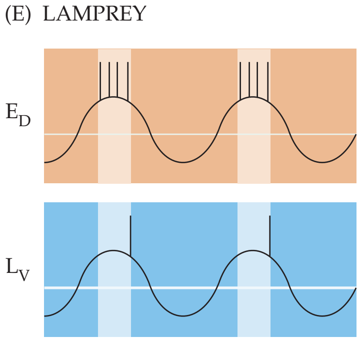




(C) In the lamprey, as this diagram indicates, the pattern of activity across segments is also highly coordinated. (D) The elements of the central pattern generator in the lamprey have been worked out in detail, providing a guide to understanding homologous circuitry in more complex spinal cords.
(E) As in the leech, different patterns of electrical activity in lamprey spinal neurons (neurons E_D and L_V in this example) correspond to distinct periods in the sequence of muscle contractions related to the swim cycle.



tic than the fibrils of the tendon. When a muscle actively contracts, however, the force acts directly on the tendon, leading to an increase in the tension of the collagen fibrils in the tendon organ and compression of the intertwined sensory receptors. As a result, Golgi tendon organs are exquisitely sensitive to increases in muscle *tension* that arise from muscle contraction but, unlike spindles, are relatively insensitive to *passive stretch* (Figure 15.11B).

The Ib axons from Golgi tendon organs contact inhibitory local circuit neurons in the spinal cord (called Ib inhibitory interneurons) that synapse, in turn, with the α motor neurons that innervate the same muscle. The Golgi tendon circuit is thus a negative feedback system that regulates muscle tension; it decreases the activation of a muscle when exceptionally large forces are generated and this way protects the muscle. This reflex circuit also operates at reduced levels of muscle force, counteracting small changes in muscle tension by increasing or decreasing the inhibition of α motor neurons. Under these conditions, the Golgi tendon system tends to maintain a steady level of force, counteracting effects that diminish muscle force (such as fatigue). In short, the muscle spindle system is a feedback system that monitors and maintains muscle *length*, and the Golgi tendon system is a feedback system that monitors and maintains muscle *force*.

Like the muscle spindle system, the Golgi tendon organ system is not a closed loop. The Ib inhibitory interneurons also receive synaptic inputs from a variety of other sources, including cutaneous receptors, joint receptors, muscle spindles, and descending upper motor neuron pathways (Figure 15.12). Acting in concert, these inputs regulate the responsiveness of Ib interneurons to activity arising in Golgi tendon organs.

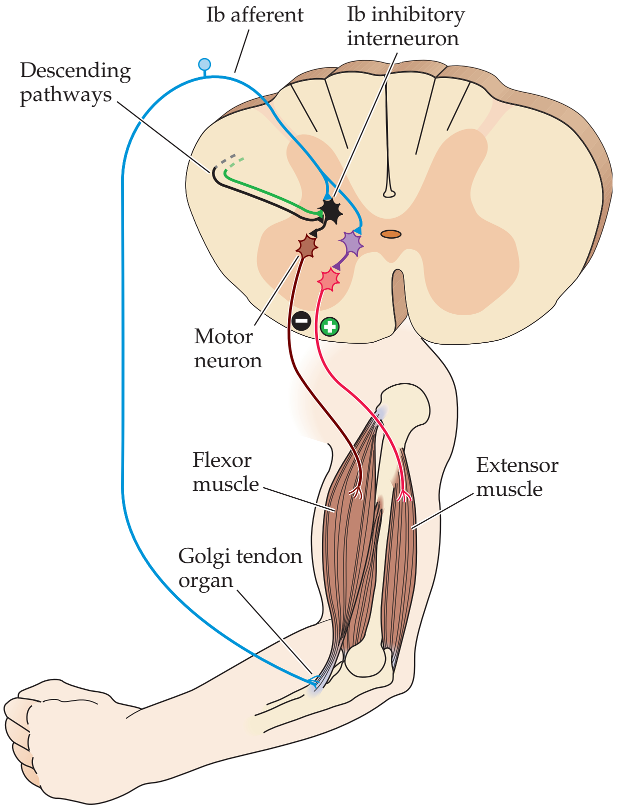


Figure 15.12 Negative feedback regulation of muscle tension by Golgi tendon organs. The Ib afferents from tendon organs contact inhibitory interneurons that decrease the activity of α motor neurons innervating the same muscle. The Ib inhibitory interneurons also receive input from other sensory fibers, as well as from descending pathways. This arrangement prevents muscles from generating excessive tension.

Flexion Reflex Pathways

So far, the discussion has focused on reflexes driven by sensory receptors located within muscles or tendons. Other reflex circuitry mediates the withdrawal of a limb from a painful stimulus, such as a pinprick or the heat of a flame. Contrary to what might be imagined given the speed with which we are able to withdraw from a painful stimulus, this **flexion reflex** involves several synaptic links (Figure 15.13). As a result of activity in this circuitry, stimulation of nociceptive sensory fibers leads to withdrawal of the limb from the source of pain by excitation of ipsilateral flexor muscles and reciprocal inhibition of ipsilateral extensor muscles. Flexion of the stimulated limb is also accompanied by an opposite reaction in the contralateral limb (i.e., the contralateral extensor muscles are excited while flexor muscles are inhibited). This **crossed extension reflex** provides postural support during withdrawal of the affected limb from the painful stimulus.

Like the other reflex pathways, local circuit neurons in the flexion reflex pathway receive converging inputs from several different sources, including other spinal cord interneurons and upper motor neuron pathways. Although the functional significance of this complex pattern of connectivity is unclear, changes in the character of the reflex following damage to descending pathways provides some insight. Under normal conditions, a noxious stimulus is required to evoke the flexion reflex; following damage to descending pathways, however, other types of stimulation, such as squeezing a limb, can sometimes produce the same response. This observation suggests that the descending projections to the spinal cord modulate the responsiveness of the local circuitry to a variety of sensory inputs.

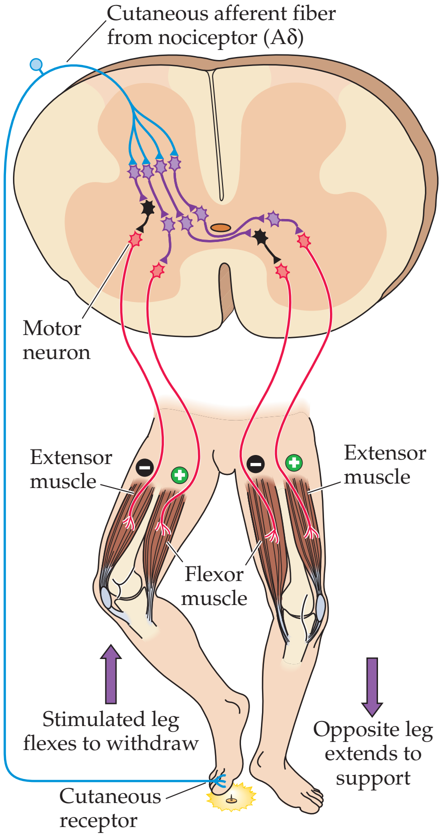

Cutaneous afferent fiber from nociceptor (Aδ)
Motor neuron
Extensor muscle
Extensor muscle
Flexor muscle
Stimulated leg flexes to withdraw
Opposite leg extends to support
Cutaneous receptor

Figure 15.13 Spinal cord circuitry responsible for the flexion reflex. Stimulation of cutaneous receptors in the foot (by stepping on a tack in this example) leads to activation of spinal cord local circuits that withdraw (flex) the stimulated extremity and extend the other extremity to provide compensatory support.

Spinal Cord Circuitry and Locomotion

The contribution of local circuitry to motor control is not, of course, limited to reflexive responses to sensory inputs. Studies of rhythmic movements such as locomotion and swimming in animal models (Box A) have demonstrated that local circuits in the spinal cord called **central pattern generators** are fully capable of controlling the timing and coordination of such complex patterns of movement, and of adjusting them in response to altered circumstances (Box B).

A good example is locomotion (walking, running, etc.). The movement of a single limb during locomotion can be thought of as a cycle consisting of two phases: a *stance phase*, during which the limb is extended and placed in contact with the ground to propel humans or other bipeds forward; and a *swing phase*, during which the limb is flexed to leave the ground and then brought forward to begin the next stance phase (Figure 15.14A). Increases in the speed of locomotion reduce the amount of time it takes to complete a cycle, and most of the change in cycle time is due to shortening the stance phase; the swing phase remains relatively constant over a wide range of locomotor speeds.

In quadrupeds, changes in locomotor speed are also accompanied by changes in the sequence of limb movements. At low speeds, for example, there is a back-to-front progression of leg movements, first on one side and then on the other. As the speed increases to a trot, the movements of the right forelimb and left hindlimb are synchronized (as are the movements of the left forelimb and right hindlimb). At the highest speeds (gallop), the movements of the two front legs are synchronized, as are the movements of the two hindlimbs (Figure 15.14B).

Given the precise timing of the movement of individual limbs and the coordination among limbs that are required in this process, it is natural to

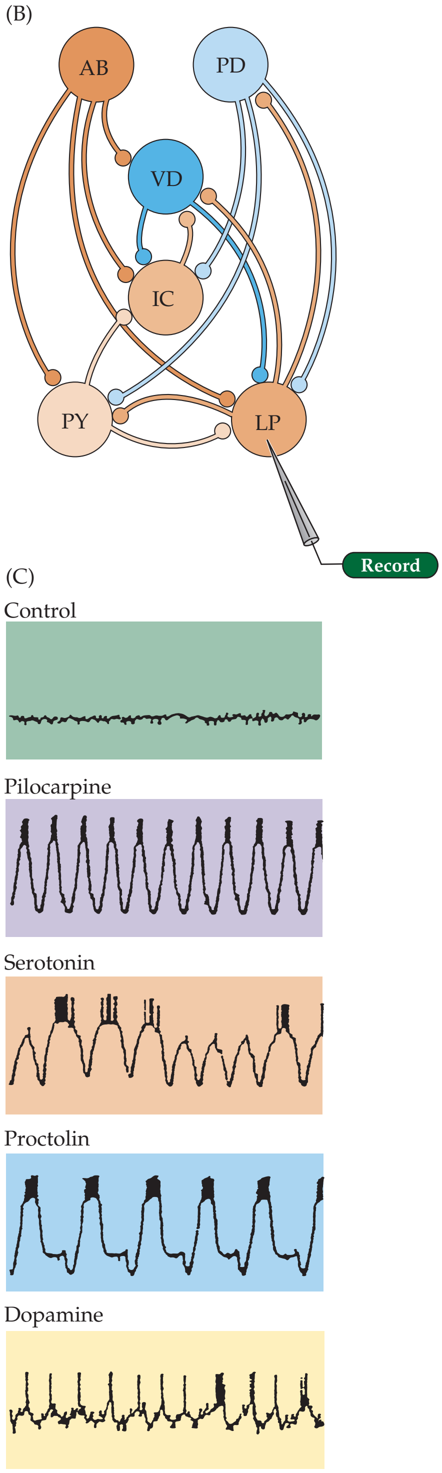
Box B

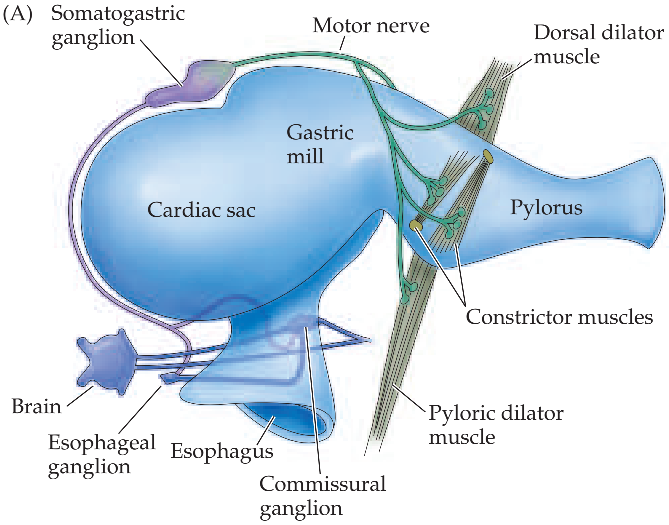
The Autonomy of Central Pattern Generators: Evidence from the Lobster Stomatogastric Ganglion

A principle that has emerged from studies of central pattern generators is that rhythmic patterns of firing elicit complex motor responses without need of ongoing sensory stimulation. A good example is the behavior mediated by a small group of nerve cells in lobsters and other crustaceans called the stomatogastric ganglion (STG) that controls the muscles of the gut (Figure A). This ensemble of 30 motor neurons and interneurons in the lobster is perhaps the most completely characterized neural circuit known. Of the 30 cells, defined subsets are essential for two distinct rhythmic movements: gastric mill movements that mediate grinding of food by "teeth" in the lobster's foregut, and pyloric movements that propel food into the hindgut. Phasic firing patterns of the motor neurons and interneurons of the STG are directly correlated with these two rhythmic movements. Each of the relevant cells has now been identified based on its position in the ganglion, and its electrophysiological and neuropharmacological properties characterized (Figures B and C).

Patterned activity in the motor neurons and interneurons of the ganglion begins only if the appropriate neuromodulatory input is provided by sensory axons that originate in other ganglia. Depending upon the activity of the sensory axons, neuronal ensembles in the STG produce one of several characteristic rhythmic firing patterns. Once activated, however, the intrinsic membrane properties of identified cells within the ensemble sustain the rhythmicity of the circuit in the absence of further sensory input.

Another key fact that has emerged from this work is that the same neurons can participate in different programmed motor activities, as circumstances


(B)
AB
PD
VD
IC
PY
LP
Record
(C)
Control
Pilocarpine
Serotonin
Proctolin
Dopamine


(A)
Somatogastric ganglion
Motor nerve
Dorsal dilator muscle
Gastric mill
Cardiac sac
Pylorus
Constrictor muscles
Brain
Esophageal ganglion
Esophagus
Commissural ganglion
Pyloric dilator muscle

(A) Location of the lobster stomatogastric ganglion in relation to the gut.
(B) Subset of identified neurons in the stomatogastric ganglion that generates gastric mill and pyloric activity. The abbreviations indicate individual identified neurons, all of which project to different pyloric muscles (except the AB neuron, which is an interneuron).
(C) Recording from one of the neurons, the lateral pyloric or LP neuron, in this circuit showing the different patterns of activity elicited by several neuromodulators known to be involved in the normal synaptic interactions in this ganglion.

demand. For example, the subset of neurons producing gastric mill activity overlaps the subset that generates pyloric activity. This economic use of neuronal subsets has not yet been described in the central pattern generators of mammals, but seems likely to be a feature of all such circuits.

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assume that locomotion is accomplished by higher centers that organize the spatial and temporal activity patterns of the individual limbs. However, following transection of the spinal cord at the thoracic level, a cat's hindlimbs will still make coordinated locomotor movements if the animal is supported and placed on a moving treadmill (Figure 15.14C). Under these conditions, the speed of locomotor movements is determined by the speed of the treadmill, suggesting that the movement is nothing more than a reflexive response to stretching the limb muscles. This possibility is ruled out, however, by experiments in which the dorsal roots are also sectioned. Although the speed of walking is slowed and the movements are less coordinated than under normal conditions, appropriate locomotor movements are still observed. These and other observations in experimental animals show that the basic rhythmic patterns of limb movement during locomotion are not dependent on sensory input; nor are they dependent on input from descending projections from higher centers. Rather, each limb appears to have its own central pattern generator responsible for the alternating flexion and extension of the limb during locomotion (see Box B). Under normal conditions, the central pattern generators for the limbs are variably coupled to each other by additional local circuits in order to achieve the different sequences of movements that occur at different speeds.

Although some locomotor movements can also be elicited in humans following damage to descending pathways, these are considerably less effective than the movements seen in the cat. The reduced ability of the transected spinal cord to mediate rhythmic stepping movements in humans presumably reflects an increased dependence of local circuitry on upper motor neuron pathways. Perhaps bipedal locomotion carries with it requirements for postural control greater than can be accommodated by spinal cord circuitry alone. Whatever the explanation, the basic oscillatory circuits that control such rhythmic behaviors as flying, walking, and swimming in many animals also play an important part in human locomotion.

The Lower Motor Neuron Syndrome

The complex of signs and symptoms that arise from damage to the lower motor neurons of the brainstem and spinal cord is referred to as the "lower motor neuron syndrome." In clinical neurology, this constellation of problems must be distinguished from the "upper motor neuron syndrome" that results from damage to the descending upper motor neuron pathways (see Chapter 16 for a discussion of the signs and symptoms associated with damage to upper motor neurons).

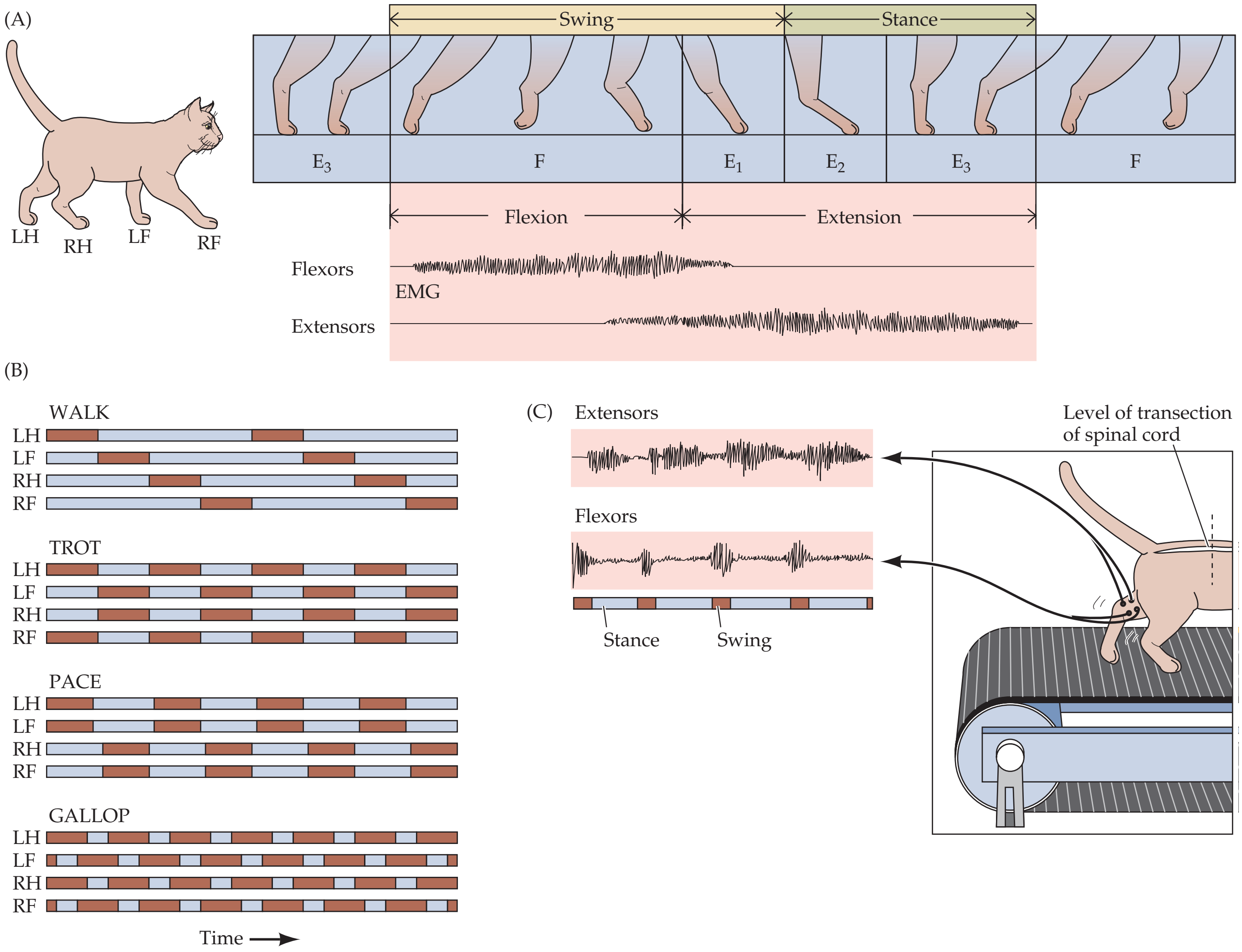

Figure 15.14 The cycle of locomotion for terrestrial mammals (a cat in this instance) is organized by central pattern generators. (A) The step cycle, showing leg flexion (F) and extension (E) and their relation to the swing and stance phases of locomotion. EMG indicates electromyographic recordings. (B) Comparison of the stepping movements for different gaits. Brown bars, foot lifted (swing phase); gray bars, foot planted (stance phase). (C) Transection of the spinal cord at the thoracic level isolates the hindlimb segments of the cord. The hindlimbs are still able to walk on a treadmill after recovery from surgery, and reciprocal bursts of electrical activity can be recorded from flexors during the swing phase and from extensors during the stance phase of walking. (After Pearson, 1976.)

Damage to lower motor neuron cell bodies or their peripheral axons results in paralysis (loss of movement) or paresis (weakness) of the affected muscles, depending on the extent of the damage. In addition to paralysis and/or paresis, the lower motor neuron syndrome includes a loss of reflexes (areflexia) due to interruption of the efferent (motor) limb of the sensory motor reflex arcs. Damage to lower motor neurons also entails a loss of muscle tone, since tone is in part dependent on the monosynaptic reflex arc that links the muscle spindles to the lower motor neurons (see also Box D in Chapter 16). A somewhat later effect is atrophy of the affected muscles due to denervation and disuse. The muscles involved may also exhibit fibrillations and fasciculations, which are spontaneous twitches characteristic of single denervated muscle fibers or motor units, respectively. These phenomena arise from changes in the excitability of denervated muscle fibers in the case of fibrillation, and from abnormal activity of injured α motor neurons in the case of fasciculations. These spontaneous contractions can be readily recognized in an electromyogram, providing an especially helpful clinical tool in diagnosing lower motor neuron disorders (Box C).

Box C
Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that affects an estimated 0.05% of the population in the United States. It is also called Lou Gehrig's disease, after the New York Yankees baseball player who died of the disorder in 1936. ALS is characterized by the slow but inexorable degeneration of α motor neurons in the ventral horn of the spinal cord and brainstem (*lower* motor neurons), and of neurons in the motor cortex (*upper* motor neurons). Affected individuals show progressive weakness due to upper and/or lower motor neuron involvement, wasting of skeletal muscles due to lower motor neuron involvement, and usually die within 5 years of onset. Sadly, these patients are condemned to watch their own demise, since the intellect remains intact. No available therapy effectively prevents the inexorable progression of this disease.

Approximately 10% of ALS cases are familial, and several distinct familial forms have been identified. An autosomal dominant form of familial ALS (FALS) is caused by mutations of the gene that encodes the cytosolic antioxidant enzyme copper/zinc superoxide dismutase (SOD1). Mutations of *SOD1* account for roughly 20% of families with FALS. A rare autosomal recessive, juvenile-onset form is caused by mutations in a protein called alsin, a putative GTPase regulator. Another rare type of FALS consists of a slowly progressive, autosomal dominant, lower motor neuron disease without sensory symptoms, with onset in early adulthood; this form is caused by mutations of a protein named dynactin.

How these mutant genes lead to the phenotype of motor neuron disease is uncertain. Defects of axonal transport have long been hypothesized to cause ALS. Evidence for this cause is that transgenic mice with mutant SOD1 exhibit defects in slow axonal transport early in the course of the disease, and that dynactin binds to microtubules and thus that mutant dynactin may modify axonal transport along microtubules. However, whether defective axonal transport is the cellular mechanism by which these mutant proteins lead to motor neuron disease remains to be clearly established. Despite these uncertainties, demonstration that mutations of each of these three genes can cause familial ALS has given scientists valuable clues about the molecular pathogenesis of at least some forms of this tragic disorder.

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Summary

Four distinct but highly interactive motor subsystems—local circuits in the spinal cord and brainstem, descending upper motor neuron pathways that control these circuits, the basal ganglia, and the cerebellum—all make essential contributions to motor control. Alpha motor neurons located in the spinal cord and in the cranial nerve nuclei in the brainstem directly link the nervous system and muscles, with each motor neuron and its associated muscle fibers constituting a functional entity called the motor unit. Motor units vary in size, amount of tension produced, speed of contraction, and degree of fatigability. Graded increases in muscle tension are mediated by both the orderly recruitment of different types of motor units and an increase in motor neuron firing frequency. Local circuitry involving sensory inputs, local circuit neurons, and α and γ motor neurons are especially important in the reflexive control of muscle activity. The stretch reflex is a monosynaptic circuit with connections between sensory fibers arising from muscle spindles and the α motor neurons that innervate the same or synergistic muscles. Gamma motor neurons regulate the gain of the stretch reflex by adjusting the level of tension in the intrafusal muscle fibers of the muscle spindle. This mechanism sets the baseline level of activity in α motor neurons and helps to regulate muscle length and tone. Other reflex circuits provide feedback control of muscle tension and mediate essential functions such as the rapid withdrawal of limbs from painful stimuli. Much of the spatial coordination and timing of muscle activation required for complex rhythmic movements such as locomotion are provided by specialized local circuits called central pattern generators. Because of their essential role in all of these circuits, damage to lower motor neurons leads to paralysis of the associated muscle and to other changes, including the loss of reflex activity, the loss of muscle tone, and eventually muscle atrophy.

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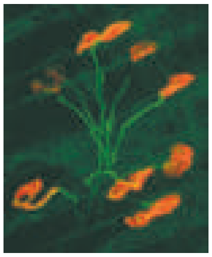
Chapter 16



Upper Motor Neuron Control of the Brainstem and Spinal Cord

Overview

The axons of upper motor neurons descend from higher centers to influence the local circuits in the brainstem and spinal cord that organize movements by coordinating the activity of lower motor neurons (see Chapter 15). The sources of these upper motor neuron pathways include several brainstem centers and a number of cortical areas in the frontal lobe. The motor control centers in the brainstem are especially important in ongoing postural control. Each center has a distinct influence. Two of these centers, the vestibular nuclear complex and the reticular formation, have widespread effects on body position. Another brainstem center, the red nucleus, controls movements of the arms; also in the brainstem, the superior colliculus contains upper motor neurons that initiate orienting movements of the head and eyes. The motor and "premotor" areas of the frontal lobe, in contrast, are responsible for the planning and precise control of complex sequences of voluntary movements. Most upper motor neurons, regardless of their source, influence the generation of movements by directly affecting the activity of the local circuits in the brainstem and spinal cord (see Chapter 15). Upper motor neurons in the cortex also control movement indirectly, via pathways that project to the brainstem motor control centers, which, in turn, project to the local organizing circuits in the brainstem and cord. A major function of these indirect pathways is to maintain the body's posture during cortically initiated voluntary movements.

Descending Control of Spinal Cord Circuitry: General Information

Some insight into the functions of the different sources of the upper motor neurons is provided by the way the lower motor neurons and local circuit neurons—the ultimate targets of the upper motor neurons—are arranged within the spinal cord. As described in Chapter 15, lower motor neurons in the ventral horn of the spinal cord are organized in a somatotopic fashion: The most medial part of the ventral horn contains lower motor neuron pools that innervate axial muscles or proximal muscles of the limbs, whereas the more lateral parts contain lower motor neurons that innervate the distal muscles of the limbs. The local circuit neurons, which lie primarily in the intermediate zone of the spinal cord and supply much of the direct input to the lower motor neurons, are also topographically arranged. Thus, the medial region of the intermediate zone of the spinal cord gray matter contains the local circuit neurons that synapse with lower motor neurons in the medial part of the ventral horn, whereas the lateral regions of the intermediate zone contain local neurons that synapse primarily with lower motor neurons in the lateral ventral horn.

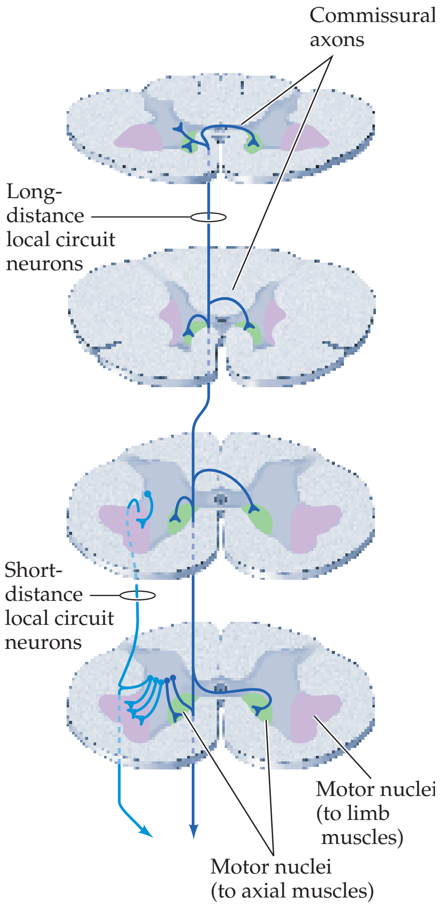

Commissural axons
Long-distance local circuit neurons
Short-distance local circuit neurons
Motor nuclei (to limb muscles)
Motor nuclei (to axial muscles)

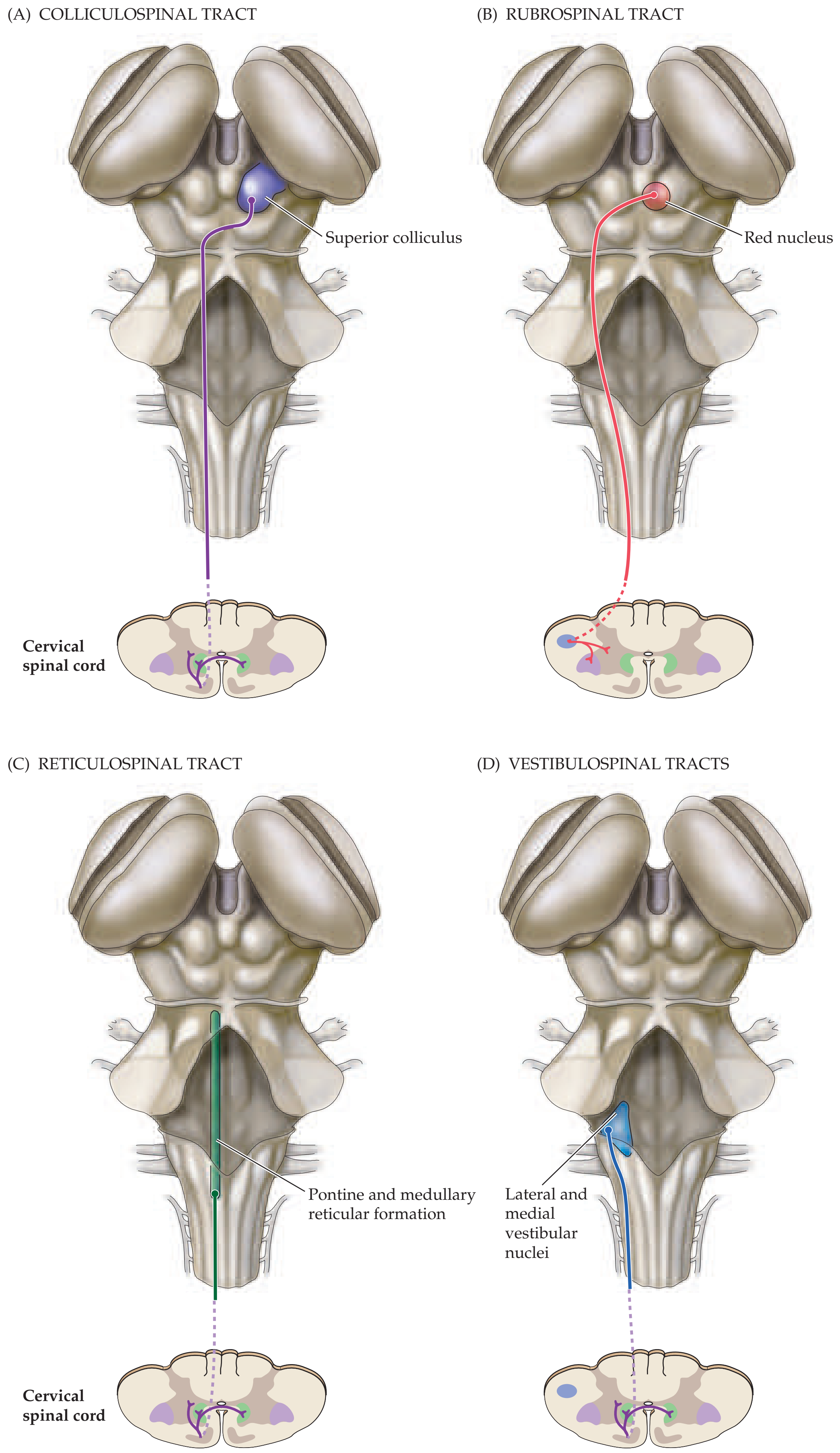
Figure 16.1 Local circuit neurons that supply the medial region of the ventral horn are situated medially in the intermediate zone of the spinal cord gray matter and have axons that extend over a number of spinal cord segments and terminate bilaterally. In contrast, local circuit neurons that supply the lateral parts of the ventral horn are located more laterally, have axons that extend over a few spinal cord segments, and terminate only on the same side of the cord. Descending pathways that contact the medial parts of the spinal cord gray matter are involved primarily in the control of posture; those that contact the lateral parts are involved in the fine control of the distal extremities.

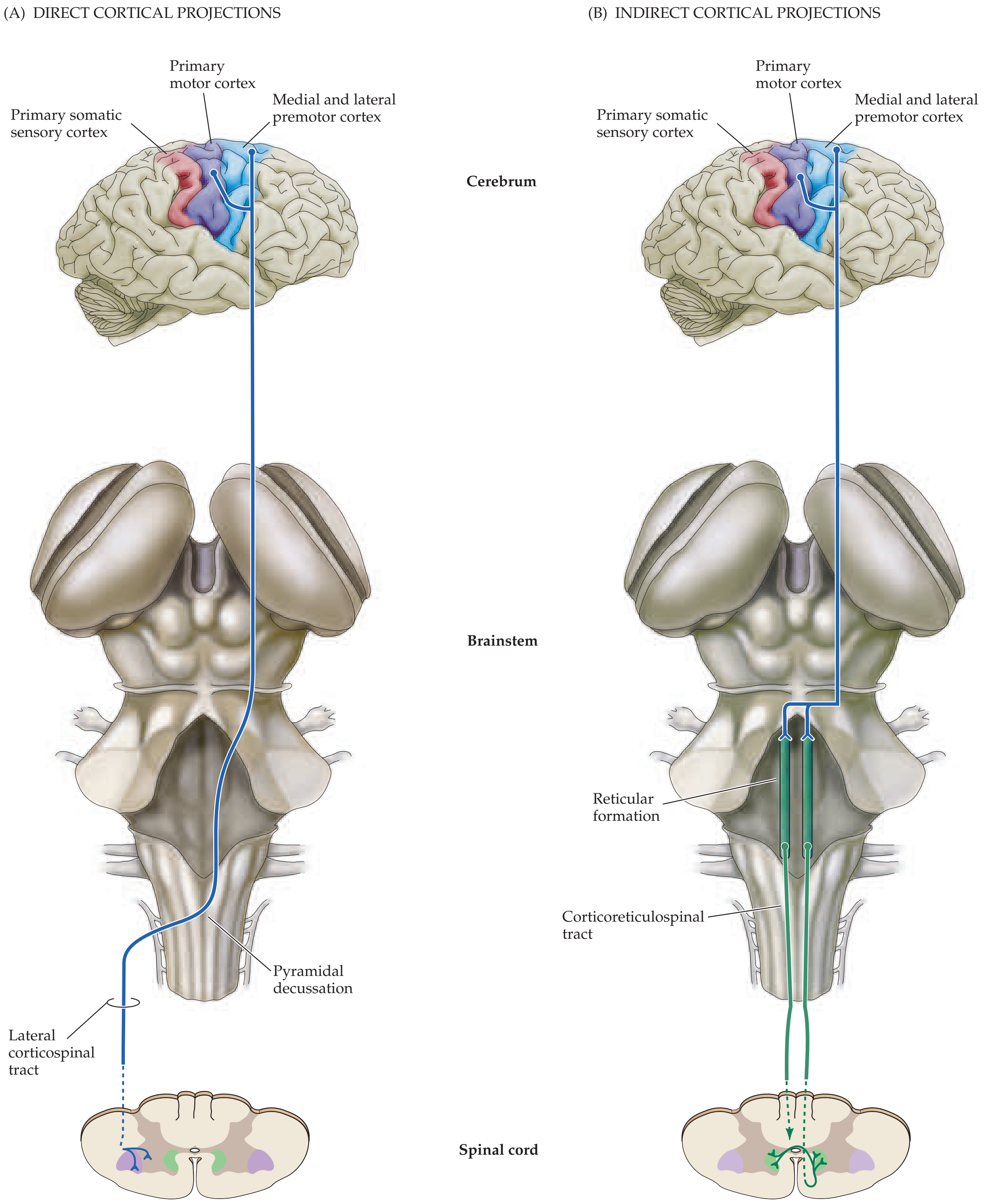
The patterns of connections made by local circuit neurons in the medial region of the intermediate zone are different from the patterns made by those in the lateral region, and these differences are related to their respective functions (Figure 16.1). The medial local circuit neurons, which supply the lower motor neurons in the medial ventral horn, have axons that project to many spinal cord segments; indeed, some project to targets along the entire length of the cord. Moreover, many of these local circuit neurons also have axonal branches that cross the midline in the commissure of the spinal cord to innervate lower motor neurons in the medial part of the contralateral hemicord. This arrangement ensures that groups of axial muscles on both sides of the body act in concert to maintain and adjust posture. In contrast, local circuit neurons in the lateral region of the intermediate zone have shorter axons that typically extend fewer than five segments and are predominantly ipsilateral. This more restricted pattern of connectivity underlies the finer and more differentiated control that is exerted over the muscles of the distal extremities, such as that required for the independent movement of individual fingers during manipulative tasks.

Differences in the way upper motor neuron pathways from the cortex and brainstem terminate in the spinal cord conform to these functional distinctions between the local circuits that organize the activity of axial and distal muscle groups. Thus, most upper motor neurons that project to the medial part of the ventral horn also project to the medial region of the intermediate zone; the axons of these upper motor neurons have collateral branches that terminate over many spinal cord segments, reaching medial cell groups on both sides of the spinal cord. The sources of these projections are primarily the vestibular nuclei and the reticular formation (see next section); as their terminal zones in the medial spinal cord gray matter suggest, they are concerned primarily with postural mechanisms (Figure 16.2). In contrast, descending axons from the motor cortex generally terminate in lateral parts of the spinal cord gray matter and have terminal fields that are restricted to only a few spinal cord segments (Figure 16.3). These corticospinal pathways are primarily concerned with precise movements involving more distal parts of the limbs.

Two additional brainstem structures, the superior colliculus and the red nucleus, also contribute upper motor neuron pathways to the spinal cord (*rubro* means red; the adjective is derived from the rich capillary bed that gives the nucleus a reddish color in fresh tissue). The axons arising from the superior colliculus project to medial cell groups in the cervical cord, where they influence the lower motor neuron circuits that control axial musculature of the neck (see Figure 16.2). These projections are particularly important in generating orienting movements of the head (the role of the superior colliculus in the generation of head and eye movements is covered in detail in Chapter 19). The red nucleus projections are also limited to the cervical level of the cord, but these terminate in lateral regions of the ventral horn and intermediate zone (see Figure 16.2). The axons arising from the red nucleus participate together with lateral corticospinal tract axons in the control of the arms. The limited distribution of rubrospinal projections may seem surprising, given the large size of the red nucleus in humans. In fact,

Figure 16.2 Descending projections from the brainstem to the spinal cord. Pathways that influence motor neurons in the medial part of the ventral horn originate in the reticular formation, vestibular nucleus, and superior colliculus. Those that influence motor neurons that control the proximal arm muscles originate in the red nucleus and terminate in more lateral parts of the ventral horn.


(A) COLLICULOSPINAL TRACT
Superior colliculus
Cervical spinal cord
(B) RUBROSPINAL TRACT
Red nucleus
(C) RETICULOSPINAL TRACT
Pontine and medullary reticular formation
Cervical spinal cord
(D) VESTIBULOSPINAL TRACTS
Lateral and medial vestibular nuclei


(A) DIRECT CORTICAL PROJECTIONS
(B) INDIRECT CORTICAL PROJECTIONS
Primary motor cortex
Primary somatic sensory cortex
Medial and lateral premotor cortex
Primary motor cortex
Primary somatic sensory cortex
Medial and lateral premotor cortex
Cerebrum
Brainstem
Pyramidal decussation
Lateral corticospinal tract
Reticular formation
Corticoreticulospinal tract
Spinal cord

◀ **Figure 16.3** Direct and indirect pathways from the motor cortex to the spinal cord. Neurons in the motor cortex that supply the lateral part of the ventral horn (A) to initiate movements of the distal limbs also terminate on neurons in the reticular formation (B) to mediate postural adjustments that support the movement. The reticulospinal pathway terminates in the medial parts of the ventral horn, where lower motor neurons that innervate axial muscles are located. Thus, the motor cortex has both direct and indirect routes by which it can influence the activity of spinal cord neurons.

sylvius

the bulk of the red nucleus in humans is a subdivision that does not project to the spinal cord at all, but relays information from the cortex to the cerebellum (see Chapter 18).

Motor Control Centers in the Brainstem: Upper Motor Neurons That Maintain Balance and Posture

As described in Chapter 13, the **vestibular nuclei** are the major destination of the axons that form the vestibular division of the eighth cranial nerve; as such, they receive sensory information from the semicircular canals and the otolith organs that specifies the position and angular acceleration of the head. Many of the cells in the vestibular nuclei that receive this information are upper motor neurons with descending axons that terminate in the medial region of the spinal cord gray matter, although some extend more laterally to contact the neurons that control the proximal muscles of the limbs. The projections from the vestibular nuclei that control axial muscles and those that influence proximal limb muscles originate from different cells and take different routes (called the medial and lateral vestibulospinal tracts). Other upper motor neurons in the vestibular nuclei project to lower motor neurons in the cranial nerve nuclei that control eye movements (the third, fourth, and sixth cranial nerve nuclei). This pathway produces the eye movements that maintain fixation while the head is moving (see Chapters 13 and 19).

The **reticular formation** is a complicated network of circuits located in the core of the brainstem that extends from the rostral midbrain to the caudal medulla and is similar in structure and function to the intermediate gray matter in the spinal cord (see Figure 16.4 and Box A). Unlike the well-defined sensory and motor nuclei of the cranial nerves, the reticular formation comprises clusters of neurons scattered among a welter of interdigitating axon bundles; it is therefore difficult to subdivide anatomically. The neurons within the reticular formation have a variety of functions, including cardiovascular and respiratory control (see Chapter 20), governance of myriad sensory motor reflexes (see Chapter 15), the organization of eye movements (see Chapter 19), regulation of sleep and wakefulness (see Chapter 27), and, most important for present purposes, the temporal and spatial coordination of movements. The descending motor control pathways from the reticular formation to the spinal cord are similar to those of the vestibular nuclei; they terminate primarily in the medial parts of the gray matter where they influence the local circuit neurons that coordinate axial and proximal limb muscles (see Figure 16.2).

Both the vestibular nuclei and the reticular formation provide information to the spinal cord that maintains posture in response to environmental (or self-induced) disturbances of body position and stability. As expected, the vestibular nuclei make adjustments in posture and equilibrium in response to infor-

Box A

The Reticular Formation

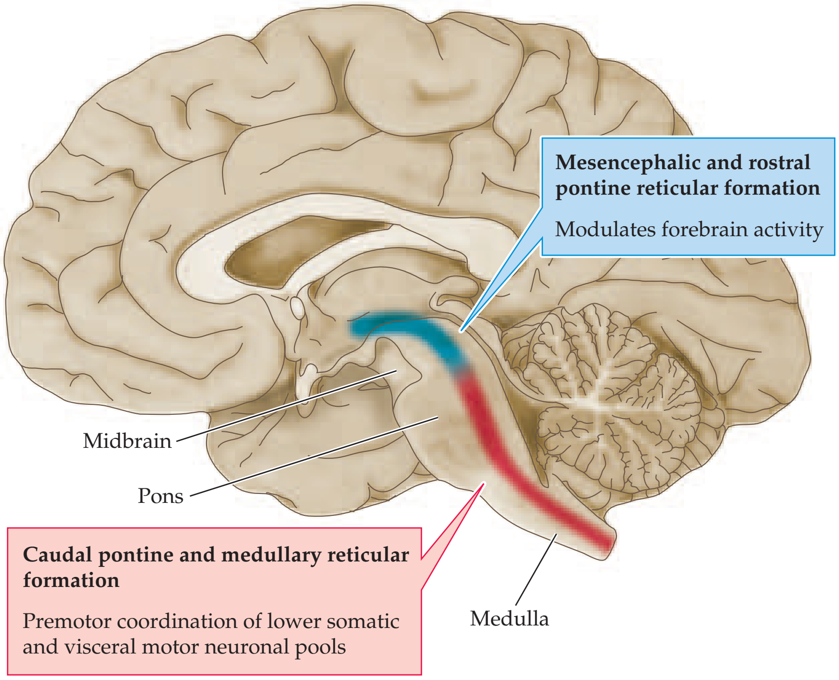
If one were to exclude from the structure of the brainstem the cranial nerve nuclei, the nuclei that provide input to the cerebellum, the long ascending and descending tracts that convey explicit sensory and motor signals, and the structures that lie dorsal and lateral to the ventricular system, what would be left is a central core region known as the *tegmentum* (Latin for "covering structure"), so named because it "covers" the ventral part of the brainstem. Scattered among the diffuse fibers that course through the tegmentum are small clusters of neurons that are collectively known as the reticular formation. With few exceptions, these clusters of neurons are difficult to recognize as distinct nuclei in standard histological preparations. Indeed, the modifying term *reticular* ("like a net") was applied to this loose collection of neuronal clusters because the early neurohistologists envisioned these neurons as part of a sparse network of diffusely connected cells that extends from the intermediate gray regions of the cervical spinal cord to the lateral regions of the hypothalamus and certain nuclei along the midline of the thalamus.

These early anatomical concepts were influenced by lesion experiments in animals and clinical observations in human patients made in the 1930s and 40s. These studies showed that damage to the upper brainstem tegmentum produced coma, suggesting the existence of a neural system in the midbrain and rostral pons that supported normal conscious brain states and transitions between sleep and wakefulness. These ideas were articulated most influentially by G. Moruzzi and H. Magoun when they proposed a "reticular activating system" to account for these functions and the critical role of the brainstem reticular formation. Current evidence generally supports the notion of an activating function of the rostral reticular formation; however, neuroscientists now recognize the complex interplay of a variety of neurochemical systems (with diverse post synaptic effects) comprising distinct cell clusters in the rostral tegmentum, and a myriad of other functions performed by neuronal clusters in more caudal parts of the reticular formation. Thus, with the advent of more precise means of demonstrating anatomical connections, as well as more sophisticated means of identifying neurotransmitters and the activity patterns of individual neurons, the concept of a "sparse network" engaged in a common function is now obsolete.

Nevertheless, the term *reticular formation* remains, as does the daunting challenge of understanding the anatomical complexity and functional heterogeneity of this complex brain region. Fortunately, two simplfying generalizations can be made. First, the functions of the different clusters of neurons in the reticular formation can be grouped into two broad categories: *modulatory functions* and *premotor functions*. Second, the modulatory functions are primarily found in the rostral sector of the reticular formation, whereas the premotor functions are localized in more caudal regions.

Several clusters of large ("magnocellular") neurons in the midbrain and rostral pontine reticular formation participate—together with certain diencephalic nuclei—in the modulation of conscious states (see Chapter 27). These effects are accomplished by long-range, diencephalic projections of cholinergic neurons near the superior cerebellar peduncle, as well as the more widespread forebrain projections of noradrenergic neurons in the locus coeruleus and serotenergic neurons in the raphe nuclei. Generally speaking, these biogenic amine neurotransmitters function as neuromodulators (see Chapter 6) that alter the membrane potential and thus the firing patterns of thalamocortical and cortical neurons (the details of these effects are explained in Chapter 27). Also included in this category are the dopaminergic systems of the ventral midbrain that modulate cortico-striatal interactions in the basal ganglia (see Chapter 17) and the responsiveness of neurons in the prefrontal cortex and limbic forebrain (see Chapter 28). However, not all modulatory projections from the rostral reticular formation are directed toward the forebrain. Although not always considered part of the reticular formation, it is helpful to include in this functional group certain neuronal columns in the periaqueductal gray (surrounding the cerebral aqueduct) that project to the dorsal horn of the spinal cord and modulate the transmission of nociceptive signals (see Chapter 9).

Reticular formation neurons in the caudal pons and medulla oblongata generally serve a premotor function in the sense that they intergate feedback sensory signals with executive commands from upper motor neurons and deep cerebellar nuclei and, in turn, organize the efferent activities of lower visceral motor and certain somatic motor neurons in the brainstem and spinal cord. Examples of this functional category include the smaller ("parvocellular") neurons that coordinate a broad range of motor activities, including the gaze centers discussed in Chapter 19 and local circuit neurons near the somatic motor and branchiomotor nuclei that organize mastication, facial expressions, and a variety of reflexive orofacial behaviors such as sneezing, hiccuping, yawning, and swallowing. In addition, there are "autonomic centers" that organize the efferent activities of specific pools of primary visceral motor neurons. Included in this subgroup are distinct clusters of neurons in the ventral-lateral medulla that generate respiratory rhythms, and others that regulate the cardioinhibitory


Mesencephalic and rostral pontine reticular formation
Modulates forebrain activity
Midbrain
Pons
Caudal pontine and medullary reticular formation
Premotor coordination of lower somatic and visceral motor neuronal pools
Medulla

Midsagittal view of the brain showing the longitudinal extent of the reticular formation and highlighting the broad functional roles performed by neuronal clusters in its rostral (blue) and caudal (red) sectors.

output of neurons in the nucleus ambiguus and the dorsal motor nucleus of the vagus nerve. Still other clusters organize more complex activities that require the coordination of both somatic motor and visceral motor outflow, such as gagging and vomiting, and even laughing and crying.

One set of neuronal clusters that does not fit easily into this rostral-caudal framework is the set of neurons that give rise to the reticulospinal projections. As described in the text, these neurons are distributed in both rostral and caudal sectors of the reticular formation and they give rise to long-range projections that innervate lower motor neuronal pools in the medial ventral horn of the spinal cord. The reticulospinal inputs serve to modulate the gain of segmental reflexes involving the muscles of the trunk and proximal limbs and to initiate certain stereotypical patterns of limb movement.

In summary, the reticular formation is best viewed as a heterogeneous collection of distinct neuronal clusters in the brainstem tegmentum that either modulate the excitability of distant neurons in the forebrain and spinal cord or coordinate the firing patterns of more local lower motor neuronal pools engaged in reflexive or stereotypical somatic motor and visceral motor behavior.

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mation from the inner ear. Direct projections from the vestibular nuclei to the spinal cord ensure a rapid compensatory response to any postural instability detected by the inner ear (see Chapter 13). In contrast, the motor centers in the reticular formation are controlled largely by other motor centers in the cortex or brainstem. The relevant neurons in the reticular formation initiate adjustments that stabilize posture during ongoing movements.

The way the upper motor neurons of the reticular formation maintain posture can be appreciated by analyzing their activity during voluntary movements. Even the simplest movements are accompanied by the activation of muscles that at first glance seem to have little to do with the primary purpose of the movement. For example, Figure 16.5 shows the pattern of muscle activity that occurs as a subject uses his arm to pull on a handle in response to an auditory tone. Activity in the biceps muscle begins about 200

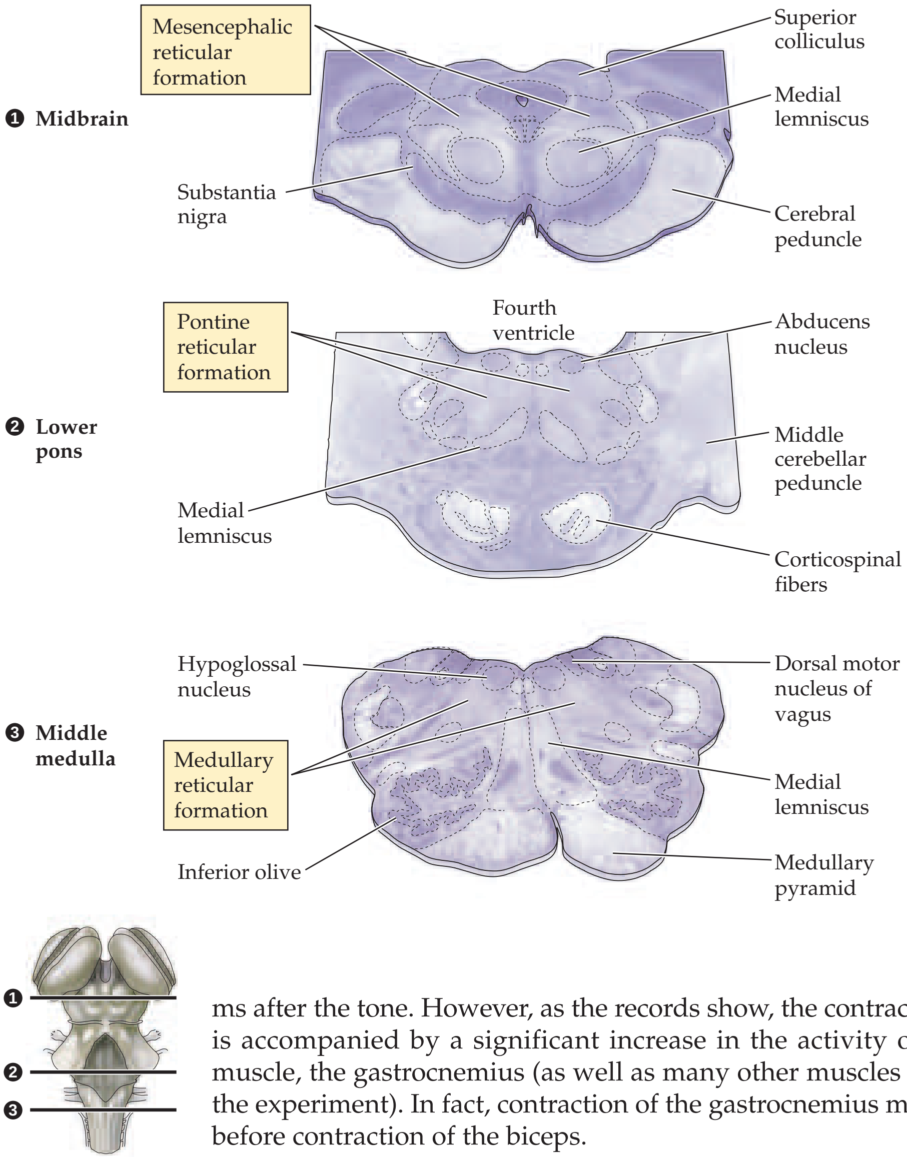

Mesencephalic reticular formation
Superior colliculus
❶ Midbrain
Medial lemniscus
Substantia nigra
Cerebral peduncle
Pontine reticular formation
Fourth ventricle
Abducens nucleus
❷ Lower pons
Middle cerebellar peduncle
Medial lemniscus
Corticospinal fibers
Hypoglossal nucleus
Dorsal motor nucleus of vagus
❸ Middle medulla
Medullary reticular formation
Medial lemniscus
Inferior olive
Medullary pyramid
❶
❷
❸

Figure 16.4 The location of the reticular formation in relation to some other major landmarks at different levels of the brainstem. Neurons in the reticular formation are scattered among the axon bundles that course through the medial portion of the midbrain, pons, and medulla (see Box A).

ms after the tone. However, as the records show, the contraction of the biceps is accompanied by a significant increase in the activity of a proximal leg muscle, the gastrocnemius (as well as many other muscles not monitored in the experiment). In fact, contraction of the gastrocnemius muscle begins well before contraction of the biceps.

These observations show that postural control entails an anticipatory, or feedforward, mechanism (Figure 16.6). As part of the motor plan for moving the arm, the effect of the impending movement on body stability is "evaluated" and used to generate a change in the activity of the gastrocnemius muscle. This change actually precedes and provides postural support for the movement of the arm. In the example given in Figure 16.5, contraction of the biceps would tend to pull the entire body forward, an action that is opposed by the contraction of the gastrocnemius muscle. In short, this feedforward mechanism "predicts" the resulting disturbance in body stability and generates an appropriate stabilizing response.

The importance of the reticular formation for feedforward mechanisms of postural control has been explored in more detail in cats trained to use a forepaw to strike an object. As expected, the forepaw movement is accompanied by feedforward postural adjustments in the other legs to maintain the animal upright. These adjustments shift the animal's weight from an even distribution over all four feet to a diagonal pattern, in which the weight is carried mostly by the contralateral, nonreaching forelimb and the ipsilateral hindlimb. Lifting of the forepaw and postural adjustments in the other limbs can also be induced in an alert cat by electrical stimulation of the motor cortex. After pharmacological inactivation of the reticular formation, however, electrical stimulation of the motor cortex evokes only the forepaw movement, without the feedforward postural adjustments that normally accompany them.

The results of this experiment can be understood in terms of the fact that the upper motor neurons in the motor cortex influence the spinal cord circuits by two routes: **direct projections** to the spinal cord and **indirect projections** to brainstem centers that in turn project to the spinal cord (see Figure 16.3). The reticular formation is one of the major destinations of these latter projections from the motor cortex; thus, cortical upper motor neurons initiate both the reaching movement of the forepaw and also the postural adjustments in the other limbs necessary to maintain body stability. The forepaw movement is initiated by the direct pathway from the cortex to the spinal cord (and possibly by the red nucleus as well), whereas the postural adjustments are mediated via pathways from the motor cortex that reach the spinal cord indirectly, after an intervening relay in the reticular formation (the corticoreticulospinal pathway).

Further evidence for the contrasting functions of the direct and indirect pathways from the motor cortex and brainstem to the spinal cord comes from experiments carried out by the Dutch neurobiologist Hans Kuypers, who examined the behavior of rhesus monkeys that had the direct pathway to the spinal cord transected at the level of the medulla, leaving the indirect descending upper motor neuron pathways to the spinal cord via the brainstem centers intact. Immediately after the surgery, the animals were able to use axial and proximal muscles to stand, walk, run, and climb, but they had great difficulty using the distal parts of their limbs (especially their hands) independently of other body movements. For example, the monkeys could cling to the cage but were unable to reach toward and pick up food with their fingers; rather, they used the entire arm to sweep the food toward them. After several weeks, the animals recovered some independent use of their hands and were again able to pick up objects of interest, but this action still involved the concerted closure of all of the fingers. The ability to make independent, fractionated movements of the fingers, as in opposing the movements of the fingers and thumb to pick up an object, never returned. These observations show that following damage to the direct corticospinal pathway at the level of the medulla, the indirect projections from the motor cortex via the brainstem centers (or from brainstem centers alone) are capable of sustaining motor behavior that involves primarily the use of proximal muscles. In contrast, the direct projections from the motor cortex to the spinal cord provide the speed and agility of movements, enabling a higher degree of precision in fractionated finger movements than is possible using the indirect pathways alone.

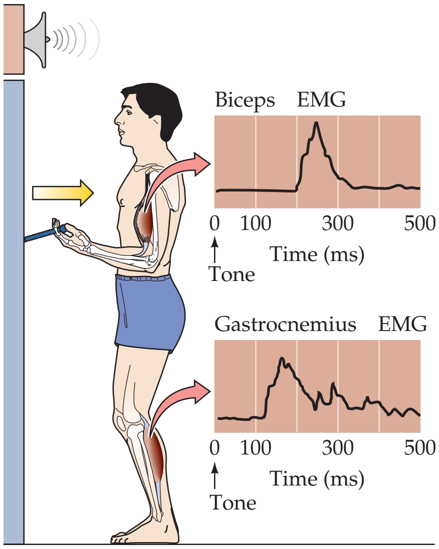


Figure 16.5 Anticipatory maintenance of body posture. At the onset of a tone, the subject pulls on a handle, contracting the biceps muscle. To ensure postural stability, contraction of the gastrocnemius muscle precedes that of the biceps. EMG refers to the electromyographic recording of muscle activity.

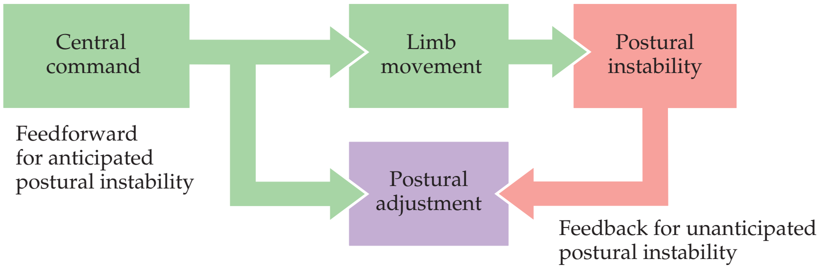

Central command
Limb movement
Postural instability
Feedforward for anticipated postural instability
Postural adjustment
Feedback for unanticipated postural instability

Figure 16.6 Feedforward and feedback mechanisms of postural control. Feedforward postural responses are "preprogrammed" and typically precede the onset of limb movement (see Figure 16.4). Feedback responses are initiated by sensory inputs that detect postural instability.

Selective damage to the corticospinal tract (i.e., the direct pathway) in humans is rarely seen in the clinic. Nonetheless, this evidence in nonhuman primates showing that direct projections from the cortex to the spinal cord are essential for the performance of discrete finger movements helps explain the limited recovery in humans after damage to the motor cortex or to the internal capsule. Immediately after such an injury, such patients are typically paralyzed. With time, however, some ability to perform voluntary movements reappears. These movements, which are presumably mediated by the brainstem centers, are crude for the most part, and the ability to perform discrete finger movements such as those required for writing, typing, or buttoning typically remains impaired.

The Corticospinal and Corticobulbar Pathways: Upper Motor Neurons That Initiate Complex Voluntary Movements

The upper motor neurons in the cerebral cortex reside in several adjacent and highly interconnected areas in the frontal lobe, which together mediate the planning and initiation of complex temporal sequences of voluntary movements. These cortical areas all receive regulatory input from the basal ganglia and cerebellum via relays in the ventrolateral thalamus (see Chapters 17 and 18), as well as inputs from the somatic sensory regions of the parietal lobe (see Chapter 8). Although the phrase "motor cortex" is sometimes used to refer to these frontal areas collectively, more commonly it is restricted to the **primary motor cortex,** which is located in the precentral gyrus (Figure 16.7). The primary motor cortex can be distinguished from the adjacent "premotor" areas both cytoarchitectonically (it is area 4 in Brodmann's nomenclature) and by the low intensity of current necessary to elicit movements by electrical stimulation in this region. The low threshold for eliciting movements is an indicator of a relatively large and direct pathway from the primary area to the lower motor neurons of the brainstem and spinal cord. This section and the next focus on the organization and functions of the primary motor cortex and its descending pathways, whereas the subsequent section addresses the contributions of the adjacent premotor areas.

The pyramidal cells of cortical layer V (also called Betz cells) are the upper motor neurons of the primary motor cortex. Their axons descend to the brainstem and spinal motor centers in the **corticobulbar** and **corticospinal tracts**, passing through the internal capsule of the forebrain to enter the cerebral peduncle at the base of the midbrain (Figure 16.8). They then

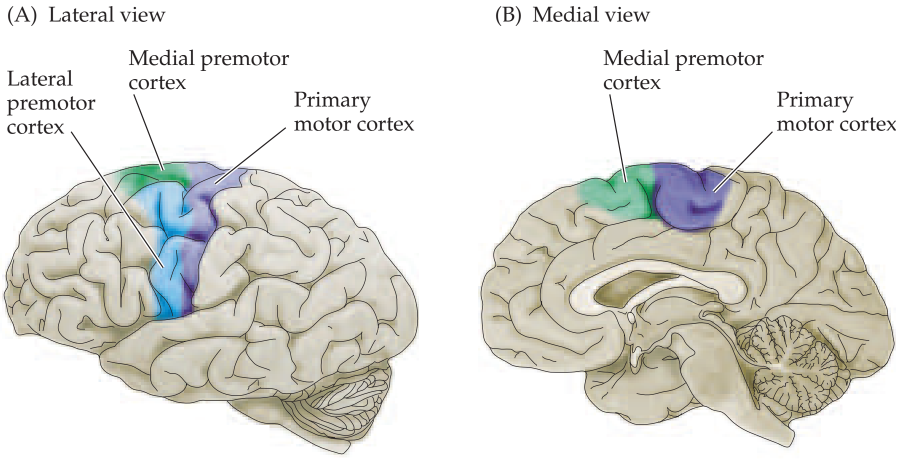


Figure 16.7 The primary motor cortex and the premotor area in the human cerebral cortex as seen in lateral (A) and medial (B) views. The primary motor cortex is located in the precentral gyrus; the premotor area is more rostral.

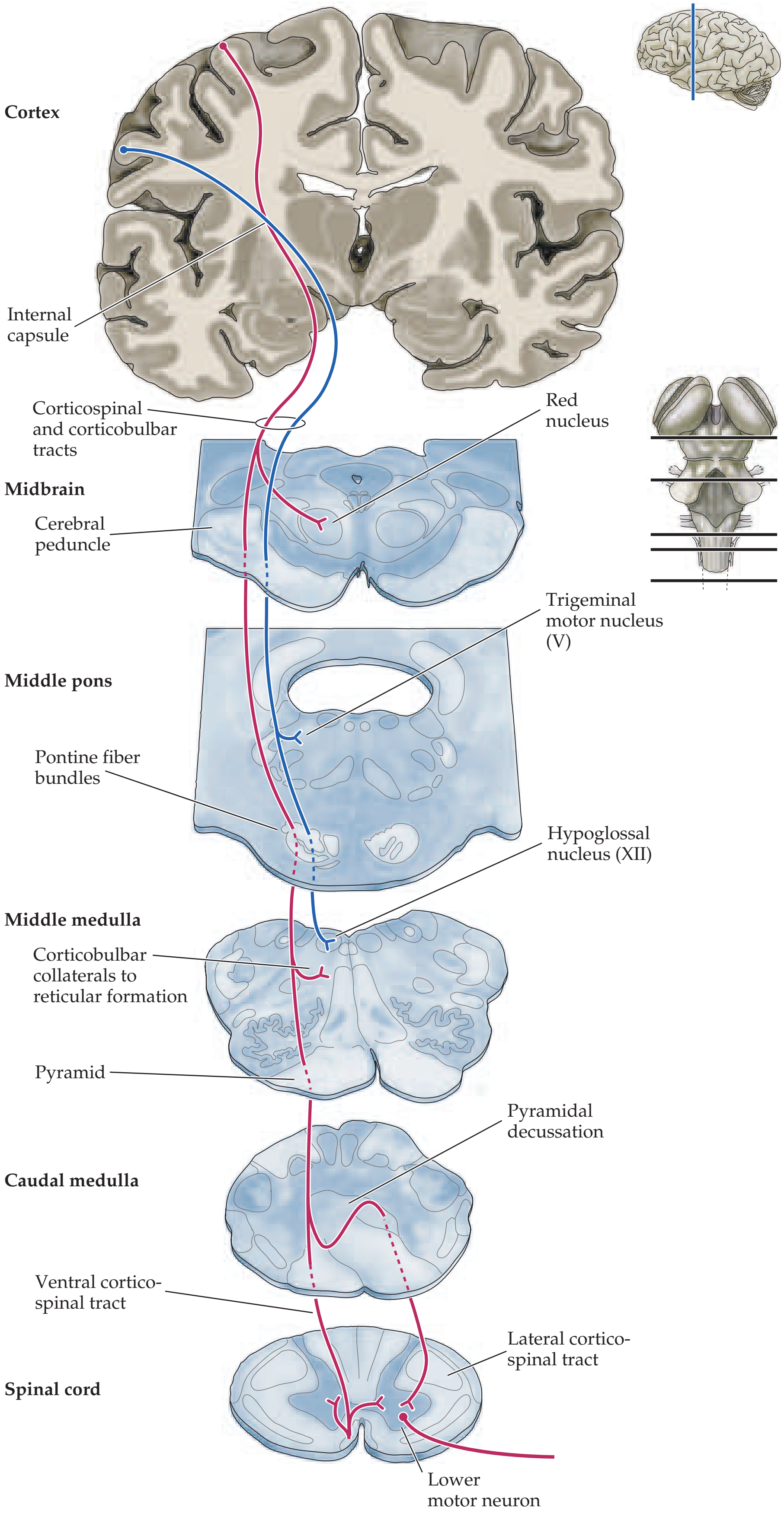

Cortex
Internal capsule
Corticospinal and corticobulbar tracts
Midbrain
Cerebral peduncle
Red nucleus
Middle pons
Trigeminal motor nucleus (V)
Pontine fiber bundles
Hypoglossal nucleus (XII)
Middle medulla
Corticobulbar collaterals to reticular formation
Pyramid
Pyramidal decussation
Caudal medulla
Ventral cortico-spinal tract
Lateral cortico-spinal tract
Spinal cord
Lower motor neuron

Figure 16.8 The corticospinal and corticobulbar tracts. Neurons in the motor cortex give rise to axons that travel through the internal capsule and coalesce on the ventral surface of the midbrain, within the cerebral peduncle. These axons continue through the pons and come to lie on the ventral surface of the medulla, giving rise to the pyramids. Most of these pyramidal fibers cross in the caudal part of the medulla to form the lateral corticospinal tract in the spinal cord. Those axons that do not cross form the ventral corticospinal tract.

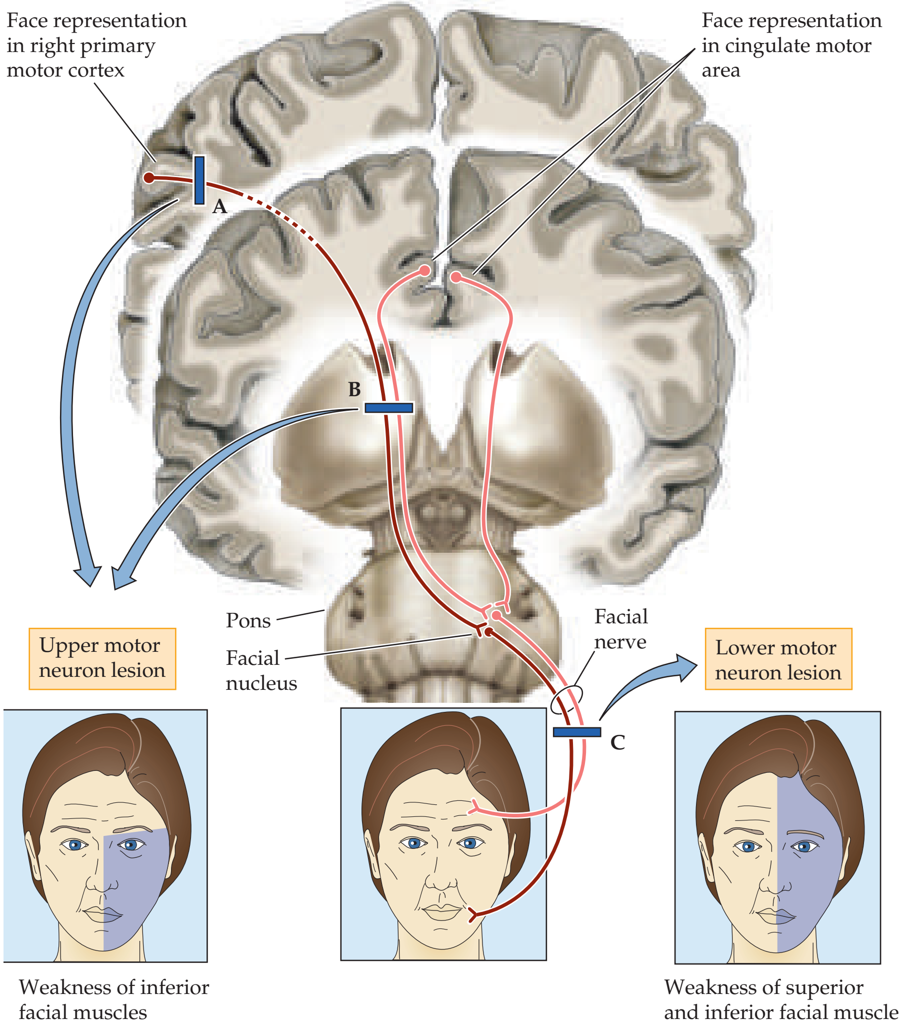
sylvius

Box B

Patterns of Facial Weakness and Their Importance for Localizing Neurological Injury

The signs and symptoms pertinent to the cranial nerves and their nuclei are of special importance to clinicians seeking to pinpoint the neurological lesions that produce motor deficits. An especially instructive example is provided by the muscles of facial expression. It has long been recognized that the distribution of facial weakness provides important localizing clues indicating whether the underlying injury involves lower motor neurons in the facial motor nucleus (and/or their axons in the facial nerve) or the inputs that govern these neurons, which arise from upper motor neurons in the cerebral cortex. Damage to the facial motor nucleus or its nerve affects all the muscles of facial expression on the side of the lesion (lesion C in the figure); this is expected given the intimate anatomical and functional linkage between lower motor neurons and skeletal muscles. A pattern of impairment that is more difficult to explain accompanies unilateral injury to the motor areas in the lateral frontal lobe (primary motor cortex, lateral premotor cortex), as occurs strokes that involve the middle cerebral artery (lesion A in the figure). Most patients with such injuries have difficulty controlling the contralateral muscles around the mouth but retain the ablility to symmetrically raise their eyebrows, wrinkle their forehead, and squint.

Until recently, it was assumed that this pattern of inferior facial paresis with superior facial sparing could be attributed to (presumed) bilateral projections from the face representation in the *primary motor cortex* to the facial motor nucleus; in this conception, the intact ipsilateral corticobulbar projections were considered sufficient to motivate the contractions of the superior muscles of the face. However, recent tract-tracing studies in non-human primates have suggested a different explanation. These studies demonstrate two important facts that clarify the relations among the face representations in the cerebral cortex and the facial motor nucleus. First, the corticobulbar projections of the primary motor cortex are directed predominantly toward the lateral cell columns in the contralateral facial motor nucleus, which control the movements of the perioral musculature. Thus, the more dorsal cell columns in the facial motor nucleus that innervate superior facial muscles do not receive significant input from the primary motor cortex. Second, these dorsal cell columns are governed by an acces-


Face representation in right primary motor cortex
Face representation in cingulate motor area
A
B
C
Pons
Facial nucleus
Facial nerve
Upper motor neuron lesion
Lower motor neuron lesion
Weakness of inferior facial muscles
Weakness of superior and inferior facial muscle

Organization of projections from cerebral cortex to the facial motor nucleus and the effects of upper and lower motor neuron lesions.

sory motor area in the anterior cingulate gyrus, a cortical region that is associated with emotional processing (see Chapter 28). Therefore, a better interpretation is that strokes involving the middle cerebral artery spare the superior aspect of the face because the relevant upper motor neurons are in the cingulum, which is supplied by the anterior cerebral artery.

An additional puzzle has also been resolved by these studies. Strokes involving the anterior cerebral artery or subcortical lesions that interrupt the corticobulbar projection (lesion B in the figure) seldom produce significant paresis of the superior facial muscles. Superior facial sparing in these situations may arise because this *cingulate motor area* sends descending projections through the corticobulbar pathway that bifuracte and innervate dorsal facial motor cell columns on both sides of the brainstem. Thus, the superior muscles of facial expression are controlled by symmetrical inputs from the cingulate motor areas in both hemispheres.

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run through the base of the pons, where they are scattered among the transverse pontine fibers and nuclei of the pontine gray matter, coalescing again on the ventral surface of the medulla where they form the **medullary pyramids**. The components of this upper motor neuron pathway that innervate cranial nerve nuclei, the reticular formation, and the red nucleus (that is, the corticobulbar tract) leave the pathway at the appropriate levels of the brainstem (see Figure 16.8 and Box B). At the caudal end of the medulla, most, but not all, of the axons in the pyramidal tract cross (or “decussate”) to enter the lateral columns of the spinal cord, where they form the **lateral corticospinal tract**. A smaller number of axons enters the spinal cord without crossing; these axons, which comprise the **ventral corticospinal tract**, terminate either ipsilaterally or contralaterally, after crossing in the midline (via spinal cord commissure). The ventral corticospinal pathway arises primarily from regions of the motor cortex that serve axial and proximal muscles.

The lateral corticospinal tract forms the direct pathway from the cortex to the spinal cord and terminates primarily in the lateral portions of the ventral horn and intermediate gray matter (see Figures 16.3 and 16.8). The indirect pathway to lower motor neurons in the spinal cord runs, as already described, from the motor cortex to two of the sources of upper motor neurons in the brainstem: the red nucleus and the reticular formation. In general, the axons to the reticular formation originate from the parts of the motor cortex that project to the medial region of the spinal cord gray matter, whereas the axons to the red nucleus arise from the parts of the motor cortex that project to the lateral region of the spinal cord gray matter.

Functional Organization of the Primary Motor Cortex

Clinical observations and experimental work dating back a hundred years or more have provided a reasonably coherent picture of the functional organization of the motor cortex. By the end of the nineteenth century, experimental work in animals by the German physiologists G. Theodor Fritsch and Eduard Hitzig had shown that electrical stimulation of the motor cortex elicits contractions of muscles on the contralateral side of the body. At about the same time, the British neurologist John Hughlings Jackson surmised that the motor cortex contains a complete representation, or map, of the body’s musculature.

Jackson reached this conclusion from his observation that the abnormal movements during some types of epileptic seizures "march" systematically from one part of the body to another. For instance, partial motor seizures may start with abnormal movements of a finger, progress to involve the entire hand, then the forearm, the arm, the shoulder, and, finally, the face.

This early evidence for motor maps in the cortex was confirmed shortly after the turn of the nineteenth century when Charles Sherrington published his classical maps of the organization of the motor cortex in great apes, using focal electrical stimulation. During the 1930s, one of Sherrington's students, the American neurosurgeon Wilder Penfield, extended this work by demonstrating that the human motor cortex also contains a spatial map of the body's musculature. By correlating the location of muscle contractions with the site of electrical stimulation on the surface of the motor cortex (the same method used by Sherrington), Penfield mapped the representation of the muscles in the precentral gyrus in over 400 neurosurgical patients (Figure 16.9). He found that this motor map shows the same disproportions observed in the somatic sensory maps in the postcentral gyrus (see Chapter 8). Thus, the musculature used in tasks requiring fine motor control (such as movements of the face and hands) occupies a greater amount of space in the

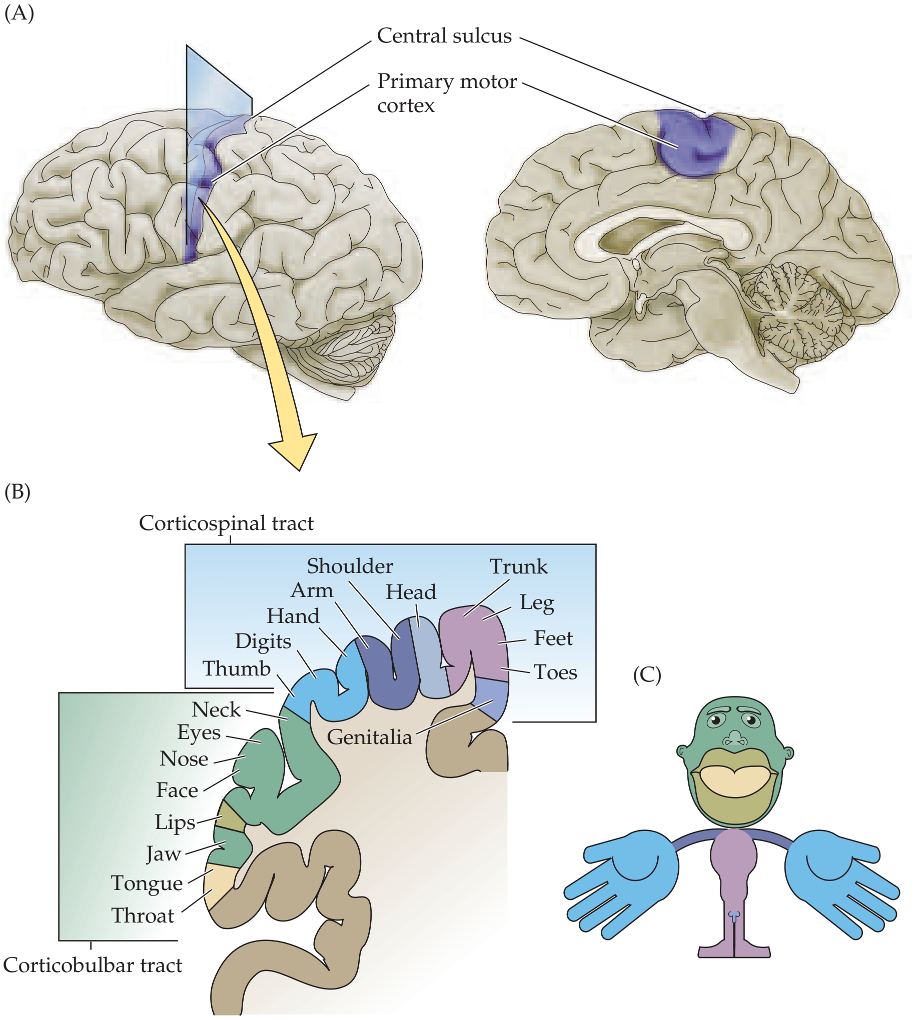

Figure 16.9 Topographic map of the body musculature in the primary motor cortex. (A) Location of primary motor cortex in the precentral gyrus. (B) Section along the precentral gyrus, illustrating the somatotopic organization of the motor cortex. The most medial parts of the motor cortex are responsible for controlling muscles in the legs; the most lateral portions are responsible for controlling muscles in the face. (C) Disproportional representation of various portions of the body musculature in the motor cortex. Representations of parts of the body that exhibit fine motor control capabilities (such as the hands and face) occupy a greater amount of space than those that exhibit less precise motor control (such as the trunk).

map than does the musculature requiring less precise motor control (such as that of the trunk). The behavioral implications of cortical motor maps are considered in Boxes C and D.

The introduction in the 1960s of intracortical microstimulation (a more refined method of cortical activation) allowed a more detailed understanding of motor maps. Microstimulation entails the delivery of electrical currents an order of magnitude smaller than those used by Sherrington and Penfield. By passing the current through the sharpened tip of a metal microelectrode inserted into the cortex, the upper motor neurons in layer V that project to lower motor neuron circuitry can be stimulated focally. Although intracortical stimulation generally confirmed Penfield's spatial map in the motor cortex, it also showed that the finer organization of the map is rather different than most neuroscientists imagined. For example, when microstimulation was combined with recordings of muscle electrical activity, even the smallest currents capable of eliciting a response initiated the excitation of several muscles (and the simultaneous inhibition of others), suggesting that organized movements rather than individual muscles are represented in the map (see Box C). Furthermore, within major subdivisions of the map (e.g., arm, forearm, or finger regions), a particular movement could be elicited by stimulation of widely separated sites, indicating that neurons in nearby regions are linked by local circuits to organize specific movements. This interpretation has been supported by the observation that the regions responsible for initiating different movements overlap substantially.

About the same time that these studies were being undertaken, Ed Evarts and his colleagues at the National Institutes of Health were pioneering a technique in which implanted microelectrodes were used to record the electrical activity of individual motor neurons in awake, behaving monkeys. In these experiments, the monkeys were trained to perform a variety of motor tasks, thus providing a means of correlating neuronal activity with voluntary movements. Evarts and his group found that the force generated by contracting muscles changed as a function of the firing rate of upper motor neurons. Moreover, the firing rates of the active neurons often changed *prior* to movements involving very small forces. Evarts therefore proposed that the primary motor cortex contributes to the initial phase of recruitment of lower motor neurons involved in the generation of finely controlled movements. Additional experiments showed that the activity of primary motor neurons is correlated not only with the magnitude, but also with the direction of the force produced by muscles. Thus, some neurons show progressively less activity as the direction of movement deviates from the neuron's "preferred direction."

A further advance was made in the mid-1970s by the introduction of spike-triggered averaging (Figure 16.10). By correlating the timing of the cortical neuron's discharges with the onset times of the contractions generated by the various muscles used in a movement, this method provides a way of measuring the influence of a single cortical motor neuron on a population of lower motor neurons in the spinal cord. Recording such activity from different muscles as monkeys performed wrist flexion or extension demonstrated that the activity of a number of different muscles is directly facilitated by the discharges of a given upper motor neuron. This peripheral muscle group is referred to as the "muscle field" of the upper motor neuron. On average, the size of the muscle field in the wrist region is two to three muscles per upper motor neuron. These observations confirmed that single upper motor neurons contact several lower motor neuron pools; the results are also consistent with the general conclusion that *movements*, rather than individual muscles,

Box C
What Do Motor Maps Represent?

Electrical stimulation studies carried out by the neurosurgeon Wilder Penfield and his colleagues in human patients (and by Sherrington and later Clinton Woolsey and his colleagues in experimental animals) clearly demonstrated a systematic map of the body's musculature in the primary motor cortex (see text). The fine structure of this map, however, has been a continuing source of controversy. Is the map in the motor cortex a "piano keyboard" for the control of individual muscles, or is it a map of movements, in which specific sites control multiple muscle groups that contribute to the generation of particular actions? Initial experiments implied that the map in the motor cortex is a fine-scale representation of individual muscles. Thus, stimulation of small regions of the map activated single muscles, suggesting that vertical columns of cells in the motor cortex were responsible for controlling the actions of particular muscles, much as columns in the somatic sensory map are thought to analyze particular types of stimulus information (see Chapter 8).

More recent studies using anatomical and physiological techniques, however, have shown that the map in the motor cortex is far more complex than a columnar representation of particular muscles. Individual pyramidal tract axons are now known to terminate on sets of spinal motor neurons that innervate different muscles. This relationship is evident even for neurons in the hand representation of the motor cortex, the region that controls the most discrete, fractionated movements. Furthermore, cortical microstimulation experiments have shown that contraction of a single muscle can be evoked by stimulation over a wide region of the motor cortex (about 2–3 mm in macaque monkeys) in a complex, mosaic fashion. It seems likely that horizontal connections within the motor cortex and local circuits in the spinal cord create ensembles of neurons that coordinate the pattern of firing in the population of ventral horn cells that ultimately generate a given movement.

Thus, while the somatotopic maps in the motor cortex generated by early studies are correct in their overall topography, the fine structure of the map is far more intricate. Unraveling these details of motor maps still holds the key to understanding how patterns of activity in the motor cortex generate a given movement.

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are encoded by the activity of the upper motor neurons in the cortex (see Box C).

Finally, the relative amount of activity across large populations of neurons appears to encode the direction of visually-guided movements. Thus, the direction of movements in monkeys could be predicted by calculating a "neuronal population vector" derived simultaneously from the discharges of upper motor neurons that are "broadly tuned" in the sense that they discharge prior to movements in many directions (Figure 16.11). These observations showed that the discharges of individual upper motor neurons cannot specify the direction of an arm movement, simply because they are tuned too broadly; rather, each arm movement must be encoded by the concurrent discharges of a large population of such neurons.

The Premotor Cortex

A complex mosaic of interconnected frontal lobe areas that lie rostral to the primary motor cortex also contributes to motor functions (see Figure 16.7). The upper motor neurons in this **premotor cortex** influence motor behavior

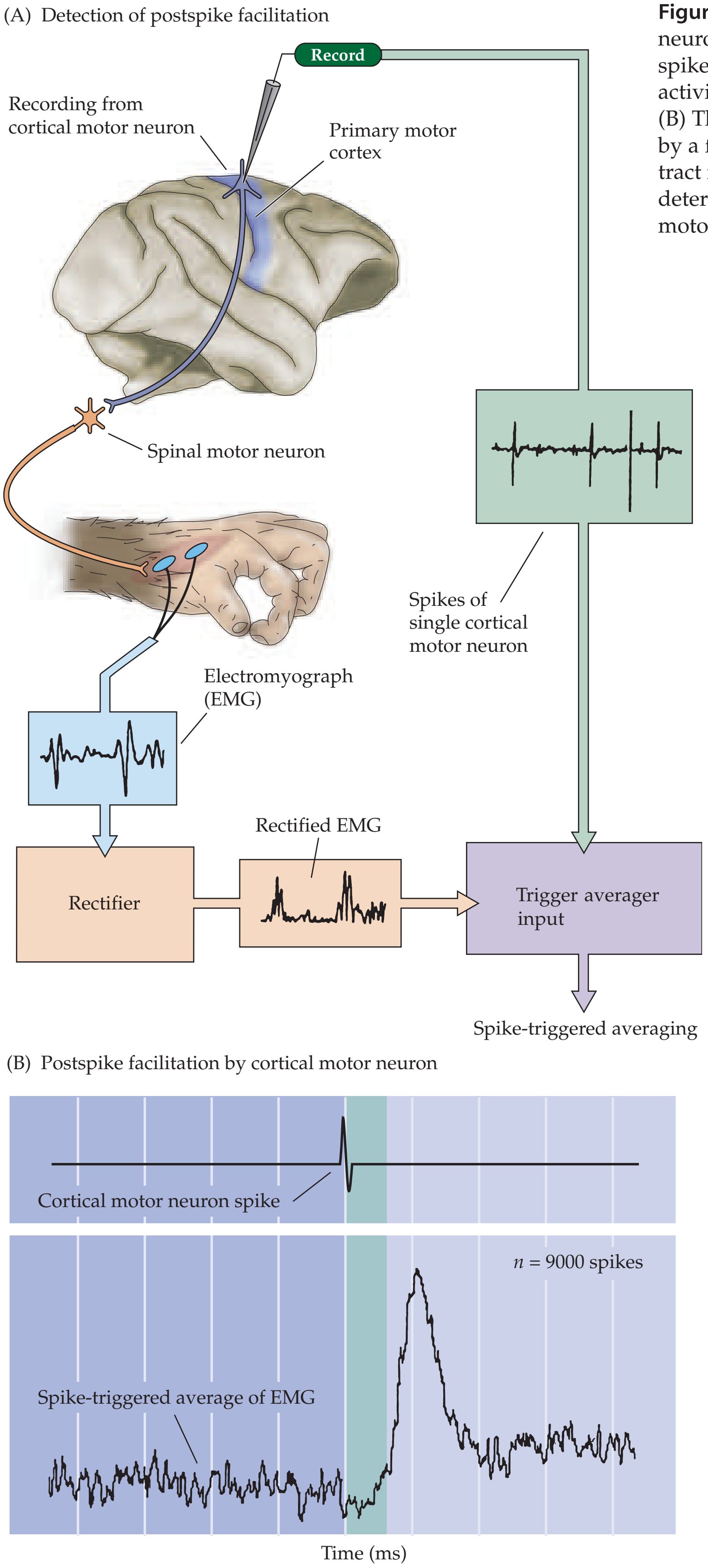
(A) Detection of postspike facilitation
Record
Recording from cortical motor neuron
Primary motor cortex
Spinal motor neuron
Spikes of single cortical motor neuron
Electromyograph (EMG)
Rectified EMG
Rectifier
Trigger averager input
Spike-triggered averaging
(B) Postspike facilitation by cortical motor neuron
Cortical motor neuron spike
n = 9000 spikes
Spike-triggered average of EMG
Time (ms)

Figure 16.10 The influence of single cortical upper motor neurons on muscle activity. (A) Diagram illustrates the spike triggering average method for correlating muscle activity with the discharges of single upper motor neurons. (B) The response of a thumb muscle (bottom trace) follows by a fixed latency the single spike discharge of a pyramidal tract neuron (top trace). This technique can be used to determine all the muscles that are influenced by a given motor neuron (see text). (After Porter and Lemon, 1993.)

Box D

Sensory Motor Talents and Cortical Space

Are special sensory motor talents, such as the exceptional speed and coordination displayed by talented athletes, ballet dancers, or concert musicians visible in the structure of the nervous system? The widespread use of noninvasive brain imaging techniques (see Box A in Chapter 1) has generated a spate of studies that have tried to answer this and related questions. Most of these studies have sought to link particular sensory motor skills to the amount of brain space devoted to such talents. For example, a study of professional violinists, cellists, and classical guitarists purported to show that representations of the "fingering" digits of the left hand in the right primary somatic sensory cortex are larger than the corresponding representations in nonmusicians.

Although such studies in humans remain controversial (the techniques are only semiquantitative), the idea that greater motor talents (or any other ability) will be reflected in a greater amount of brain space devoted to that task makes good sense. In particular, comparisons across species show that special talents are invariably based on commensurately sophisticated brain circuitry, which means more neurons, more synaptic contacts between neurons, and more supporting glial cells—all of which occupy more space within the brain. The size and proportion of bodily representations in the primary somatic sensory and motor cortices of various animals reflects species-specific nuances of mechanosensory discrimination and motor control. Thus, the representations of the paws are disproportionately large in the sensorimotor cortex of raccoons; rats and mice devote a great deal of cortical space to representations of their prominent facial whiskers; and a large fraction of the sensorimotor cortex of the star-nosed mole is given over to representing the elaborate nasal appendages that provide critical mechanosensory information for this burrowing species. The link between behavioral competence and the allocation of space is equally apparent in animals in which a particular ability has diminished, or has never developed fully, during the course of evolution.

Nevertheless, it remains uncertain how—or if—this principle applies to variations in behavior among members of the same species, including humans. For example, there does not appear to be any average hemisphere asymmetry in the allocation of space in either the primary sensory or motor area, as measured cytoarchitectonically. Some asymmetry might be expected simply because 90% of humans prefer to use the right hand when they perform challenging manual tasks. It seems likely that individual sensory motor talents among humans will be reflected in the allocation of an appreciably different amount of space to those behaviors, but this issue is just beginning to be explored with quantitative methods that are adequate to the challenge.

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both through extensive reciprocal connections with the primary motor cortex, and directly via axons that project through the corticobulbar and corticospinal pathways to influence local circuit and lower motor neurons of the brainstem and spinal cord. Indeed, over 30% of the axons in the corticospinal tract arise from neurons in the premotor cortex. In general, a variety of experiments indicate that the premotor cortex uses information from other cortical regions to select movements appropriate to the context of the action (see Chapter 25).

The functions of the premotor cortex are usually considered in terms of the lateral and medial components of this region. As many as 65% of the

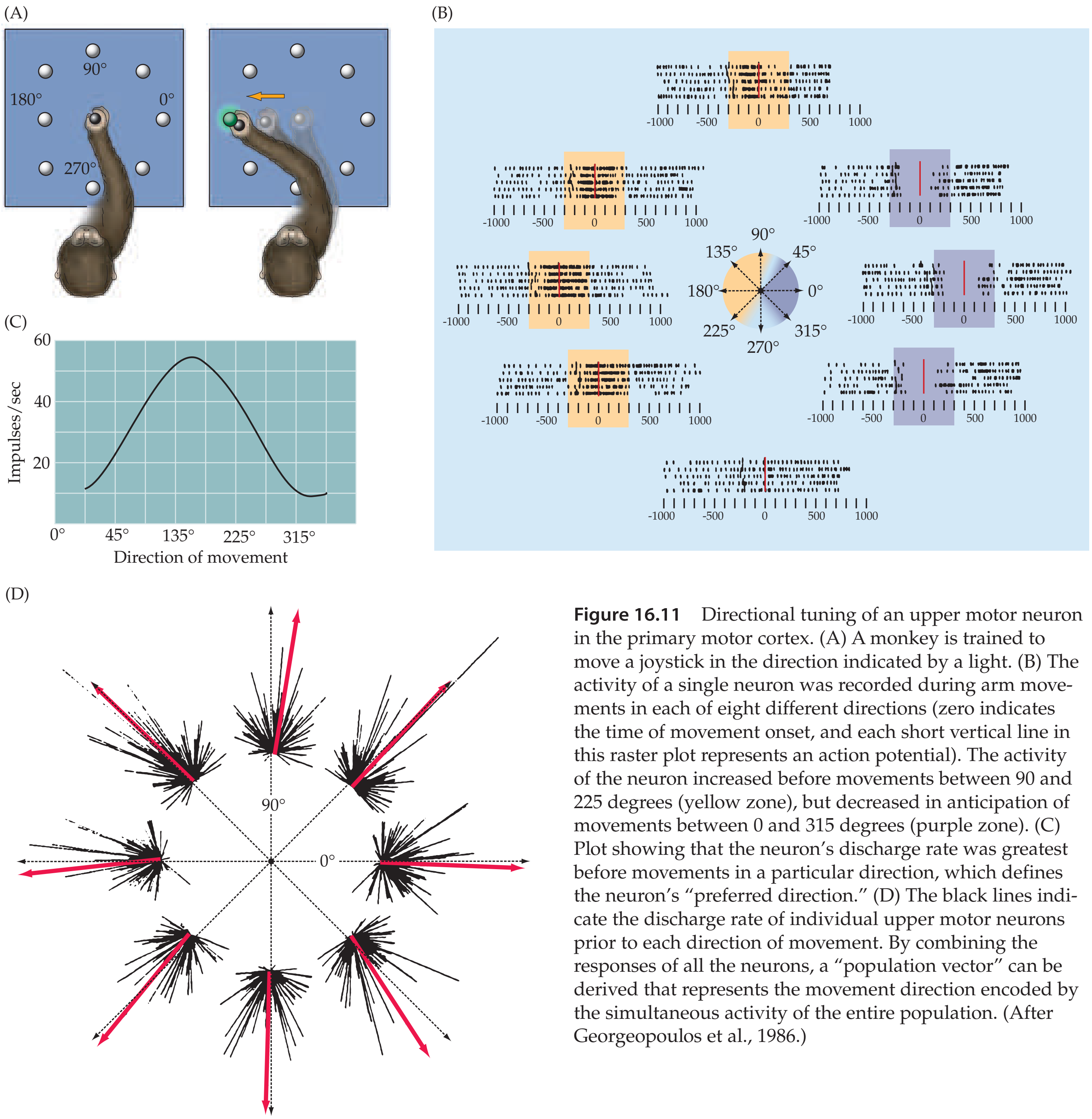

Figure 16.11 Directional tuning of an upper motor neuron in the primary motor cortex. (A) A monkey is trained to move a joystick in the direction indicated by a light. (B) The activity of a single neuron was recorded during arm movements in each of eight different directions (zero indicates the time of movement onset, and each short vertical line in this raster plot represents an action potential). The activity of the neuron increased before movements between 90 and 225 degrees (yellow zone), but decreased in anticipation of movements between 0 and 315 degrees (purple zone). (C) Plot showing that the neuron's discharge rate was greatest before movements in a particular direction, which defines the neuron's "preferred direction." (D) The black lines indicate the discharge rate of individual upper motor neurons prior to each direction of movement. By combining the responses of all the neurons, a "population vector" can be derived that represents the movement direction encoded by the simultaneous activity of the entire population. (After Georgeopoulos et al., 1986.)

neurons in the **lateral premotor cortex** have responses that are linked in time to the occurrence of movements; as in the primary motor area, many of these cells fire most strongly in association with movements made in a specific direction. However, these neurons are especially important in conditional motor tasks. That is, in contrast to the neurons in the primary motor area, when a monkey is trained to reach in different directions in response to a visual cue, the appropriately tuned lateral premotor neurons begin to fire at the appearance of the cue, well before the monkey receives a signal to actually make the movement. As the animal learns to associate a new visual cue with the movement, appropriately tuned neurons begin to increase their rate of discharge in the interval between the cue and the onset of the signal to perform the movement. Rather than directly commanding the initiation of a movement, these neurons appear to encode the monkey's *intention* to perform a particular movement; thus, they seem to be particularly involved in the *selection* of movements based on external events.

Further evidence that the lateral premotor area is concerned with movement selection comes from the effects of cortical damage on motor behavior. Lesions in this region severely impair the ability of monkeys to perform visually cued conditional tasks, even though they can still respond to the visual stimulus and can perform the same movement in a different setting. Similarly, patients with frontal lobe damage have difficulty learning to select a particular movement to be performed in response to a visual cue, even though they understand the instructions and can perform the movements. Individuals with lesions in the premotor cortex may also have difficulty performing movements in response to verbal commands.

The **medial premotor cortex,** like the lateral area, mediates the selection of movements. However, this region appears to be specialized for initiating movements specified by *internal* rather than *external* cues. In contrast to lesions in the lateral premotor area, removal of the medial premotor area in a monkey reduces the number of self-initiated or "spontaneous" movements the animal makes, whereas the ability to execute movements in response to external cues remains largely intact. Imaging studies suggest that this cortical region in humans functions in much the same way. For example, PET scans show that the medial region of the premotor cortex is activated when the subjects perform motor sequences from memory (i.e., without relying on an external instruction). In accord with this evidence, single unit recordings in monkeys indicate that many neurons in the medial premotor cortex begin to discharge one or two seconds before the onset of a self-initiated movement.

In summary, both the lateral and medial areas of the premotor cortex are intimately involved in selecting a specific movement or sequence of movements from the repertoire of possible movements. The functions of the areas differ, however, in the relative contributions of external and internal cues to the selection process.

Damage to Descending Motor Pathways: The Upper Motor Neuron Syndrome

Injury of upper motor neurons is common because of the large amount of cortex occupied by the motor areas, and because their pathways extend all the way from the cerebral cortex to the lower end of the spinal cord. Damage to the descending motor pathways anywhere along this trajectory gives rise to a set of symptoms called the **upper motor neuron syndrome**.

This clinical picture differs markedly from the lower motor neuron syndrome described in Chapter 15 and entails a characteristic set of motor deficits (Table 16.1). Damage to the motor cortex or the descending motor axons in the internal capsule causes an immediate flaccidity of the muscles on the contralateral side of the body and face. Given the topographical arrangement of the motor system, identifying the specific parts of the body

TABLE 16.1
Signs and Symptoms of Upper and Lower Motor Neuron Lesions

Upper Motor Neuron Syndrome	*Lower Motor Neuron Syndrome*
Weakness	Weakness or paralysis
Spasticity	Decreased superficial reflexes
Increased tone	Hypoactive deep reflexes
Hyperactive deep reflexes	Decreased tone
Clonus	Fasciculations and fibrillations
Babinski's sign	Severe muscle atrophy
Loss of fine voluntary movements	

that are affected helps localize the site of the injury. The acute manifestations tend to be most severe in the arms and legs: If the affected limb is elevated and released, it drops passively, and all reflex activity on the affected side is abolished. In contrast, control of trunk muscles is usually preserved, either by the remaining brainstem pathways or because of the bilateral projections of the corticospinal pathway to local circuits that control midline musculature. The initial period of "hypotonia" after upper motor neuron injury is called **spinal shock**, and reflects the decreased activity of spinal circuits suddenly deprived of input from the motor cortex and brainstem.

After several days, however, the spinal cord circuits regain much of their function for reasons that are not fully understood. Thereafter, a consistent pattern of motor signs and symptoms emerges, including:

1. *The Babinski sign*. The normal response in an adult to stroking the sole of the foot is flexion of the big toe, and often the other toes. Following damage to descending upper motor neuron pathways, however, this stimulus elicits extension of the big toe and a fanning of the other toes (Figure 16.12). A similar response occurs in human infants before the maturation of the corticospinal pathway and presumably indicates incomplete upper motor neuron control of local motor neuron circuitry.

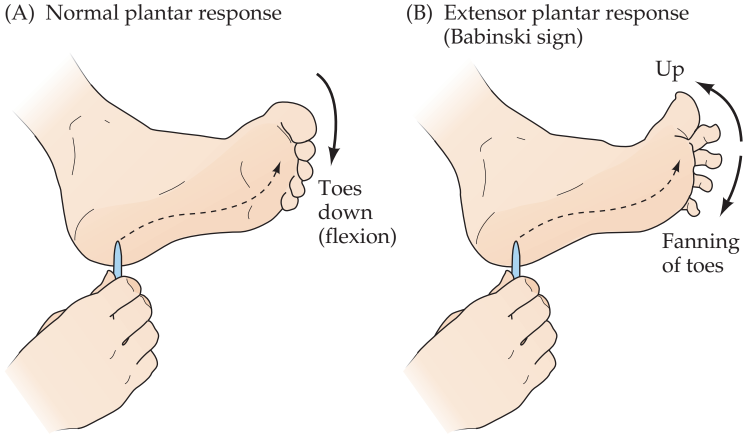
(A) Normal plantar response
Toes down (flexion)
(B) Extensor plantar response (Babinski sign)
Up
Fanning of toes

Figure 16.12 The Babinski sign. Following damage to descending corticospinal pathways, stroking the sole of the foot causes an abnormal fanning of the toes and the extension of the big toe.

Box E

Muscle Tone

Muscle tone is the resting level of tension in a muscle. In general, maintaining an appropriate level of muscle tone allows a muscle to make an optimal response to voluntary or reflexive commands in a given context. Tone in the extensor muscles of the legs, for example, helps maintain posture while standing. By keeping the muscles in a state of readiness to resist stretch, tone in the leg muscles prevents the amount of sway that normally occurs while standing from becoming too large. During activities such as walking or running, the "background" level of tension in leg muscles also helps to store mechanical energy, in effect enhancing the muscle tissue's springlike qualities. Muscle tone depends on the resting level of discharge of α motor neurons. Activity in the Ia spindle afferents—the neurons responsible for the stretch reflex—is the major contributor to this tonic level of firing. As described in Chapter 15, the γ efferent system (by its action on intrafusal muscle fibers) regulates the resting level of activity in the Ia afferents and establishes the baseline level of α motor neuron activity in the absence of muscle stretch.

Clinically, muscle tone is assessed by judging the resistance of a patient's limb to passive stretch. Damage to either the α motor neurons or the Ia afferents carrying sensory information to the α motor neurons results in a decrease in muscle tone, called hypotonia. In general, damage to descending pathways that terminate in the spinal cord has the opposite effect, leading to an increase in muscle tone, or hypertonia (except during the phase of spinal shock—see text). The neural changes responsible for hypertonia following damage to higher centers are not well understood; however, at least part of this change is due to an increase in the responsiveness of α motor neurons to Ia sensory inputs. Thus, in experimental animals in which descending inputs have been severed, the resulting hypertonia can be eliminated by sectioning the dorsal roots.

Increased resistance to passive movement following damage to higher centers is called spasticity, and is associated with two other characteristic signs: the clasp-knife phenomenon and clonus. When first stretched, a spastic muscle provides a high level of resistance to the stretch and then suddenly yields, much like the blade of a pocket knife (or clasp knife, in old-fashioned terminology). Hyperactivity of the stretch reflex loop is the reason for the increased resistance to stretch in the clasp-knife phenomenon. The physiological basis for the inhibition that causes the sudden collapse of the stretch reflex (and loss of muscle tone) is thought to involve the activation of the Golgi tendon organs (see Chapter 15).

Clonus refers to a rhythmic pattern of contractions (3–7 per second) due to the alternate stretching and unloading of the muscle spindles in a spastic muscle. Clonus can be demonstrated in the flexor muscles of the leg by pushing up on the sole of patient's foot to dorsiflex the ankle. If there is damage to descending upper motor neuron pathways, holding the ankle loosely in this position generates rhythmic contractions of both the gastrocnemius and soleus muscles. Both the increase in muscle tone and the pathological oscillations seen after damage to descending pathways are very different from the tremor at rest and cogwheel rigidity present in basal ganglia disorders such as Parkinson's disease, phenomena discussed in Chapters 17 and 18.

2. *Spasticity*. Spasticity is increased muscle tone (Box E), hyperactive stretch reflexes, and clonus (oscillatory contractions and relaxations of muscles in response to muscle stretching). Extensive upper motor neuron lesions may also be accompanied by rigidity of the extensor muscles of the leg and the flexor muscles of the arm (called decerebrate rigidity; see below). Spasticity is probably caused by the removal of inhibitory influences exerted by the cortex on the postural centers of the vestibular nuclei and reticular formation. In experimental animals, for instance, lesions of the vestibular nuclei ameliorate the spasticity that follows damage to the corticospinal tract. Spasticity is also eliminated by sectioning the dorsal roots, suggesting that it represents an abnormal increase in the *gain* of the spinal cord stretch reflexes due to loss of descending inhibition (see Chapter 15). This increased gain is also thought to explain clonus (see Box E).

3. *A loss of the ability to perform fine movements.* If the lesion involves the descending pathways that control the lower motor neurons to the upper limbs, the ability to execute fine movements (such as independent movements of the fingers) is lost.

Although these upper motor neuron signs and symptoms may arise from damage anywhere along the descending pathways, the spasticity that follows damage to descending pathways in the spinal cord is less marked than the spasticity that follows damage to the cortex or internal capsule.

For example, the extensor muscles in the legs of a patient with spinal cord damage cannot support the individual's body weight, whereas those of a patient with damage at the cortical level often can. On the other hand, lesions that interrupt the descending pathways in the brainstem above the level of the vestibular nuclei but below the level of the red nucleus cause even greater extensor tone than that which occurs after damage to higher regions. Sherrington, who first described this phenomenon, called the increased tone **decerebrate rigidity**. In the cat, the extensor tone in all four limbs is so great after lesions that spare the vestibulospinal tracts that the animal can stand without support. Patients with severe brainstem injury at the level of the pons may exhibit similar signs of decerebration, i.e., arms and legs stiffly extended, jaw clenched, and neck retracted. The relatively greater hypertonia following damage to the nervous system above the level of the spinal cord is presumably explained by the remaining activity of the intact descending pathways from the vestibular nuclei and reticular formation, which have a net excitatory influence on these stretch reflexes.

Summary

Two sets of upper motor neuron pathways make distinct contributions to the control of the local circuitry in the brainstem and spinal cord. One set originates from neurons in brainstem centers—primarily the reticular formation and the vestibular nuclei—and is responsible for postural regulation. The reticular formation is especially important in *feedforward* control of posture (that is, movements that occur in anticipation of changes in body stability). In contrast, the neurons in the vestibular nuclei that project to the spinal cord are especially important in *feedback* postural mechanisms (i.e., in producing movements that are generated in response to sensory signals that indicate an existing postural disturbance). The other major upper motor neuron pathway originates from the frontal lobe and includes projections from the primary motor cortex and the nearby premotor areas. The premotor cortices are responsible for planning and selecting movements, whereas the primary motor cortex is responsible for their execution. The motor cortex influences movements *directly* by contacting lower motor neurons and local circuit neurons in the spinal cord and brainstem, and *indirectly* by innervating neurons in brainstem centers (in this case, the reticular formation and red nucleus) that in turn project to lower motor neurons and circuits. Although the brainstem pathways can independently organize gross motor control, direct projections from the motor cortex to local circuit neurons in the brainstem and spinal cord are essential for the fine, fractionated movements of the distal parts of the limbs, the tongue, and face that are especially important in our daily lives.

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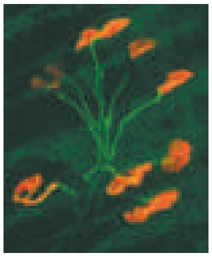
Chapter 17



Modulation of Movement by the Basal Ganglia

Overview

As described in the preceding chapter, motor regions of the cortex and brainstem contain upper motor neurons that initiate movement by controlling the activity of local circuit and lower motor neurons in the brainstem and spinal cord. This chapter and the next discuss two additional regions of the brain that are important in motor control: the basal ganglia and the cerebellum. In contrast to the components of the motor system that harbor upper motor neurons, the basal ganglia and cerebellum do not project directly to either the local circuit or lower motor neurons; instead, they influence movement by regulating the activity of upper motor neurons. The term *basal ganglia* refers to a large and functionally diverse set of nuclei that lie deep within the cerebral hemispheres. The subset of these nuclei relevant to this account of motor function includes the caudate, putamen, and the globus pallidus. Two additional structures, the substantia nigra in the base of the midbrain and the subthalamic nucleus in the ventral thalamus, are closely associated with the motor functions of these basal ganglia nuclei and are included in the discussion. The motor components of the basal ganglia, together with the substantia nigra and the subthalamic nucleus, effectively make a subcortical loop that links most areas of the cortex with upper motor neurons in the primary motor and premotor cortex and in the brainstem. The neurons in this loop respond in anticipation of and during movements, and their effects on upper motor neurons are required for the normal course of voluntary movements. When one of these components of the basal ganglia or associated structures is compromised, the patient cannot switch smoothly between commands that initiate a movement and those that terminate the movement. The disordered movements that result can be understood as a consequence of abnormal upper motor neuron activity in the absence of the supervisory control normally provided by the basal ganglia.

Projections to the Basal Ganglia

The motor nuclei of the basal ganglia are divided into several functionally distinct groups (Figure 17.1). The first and larger of these groups is called the **corpus striatum**, which includes the **caudate** and **putamen**. These two subdivisions of the corpus striatum comprise the *input* zone of the basal ganglia, their neurons being the destinations of most of the pathways that reach this complex from other parts of the brain (Figure 17.2). The name corpus striatum, which means "striped body," reflects the fact that the axon fascicles that pass through the caudate and putamen result in a striped appearance when cut in cross section. The destinations of the incoming axons from the

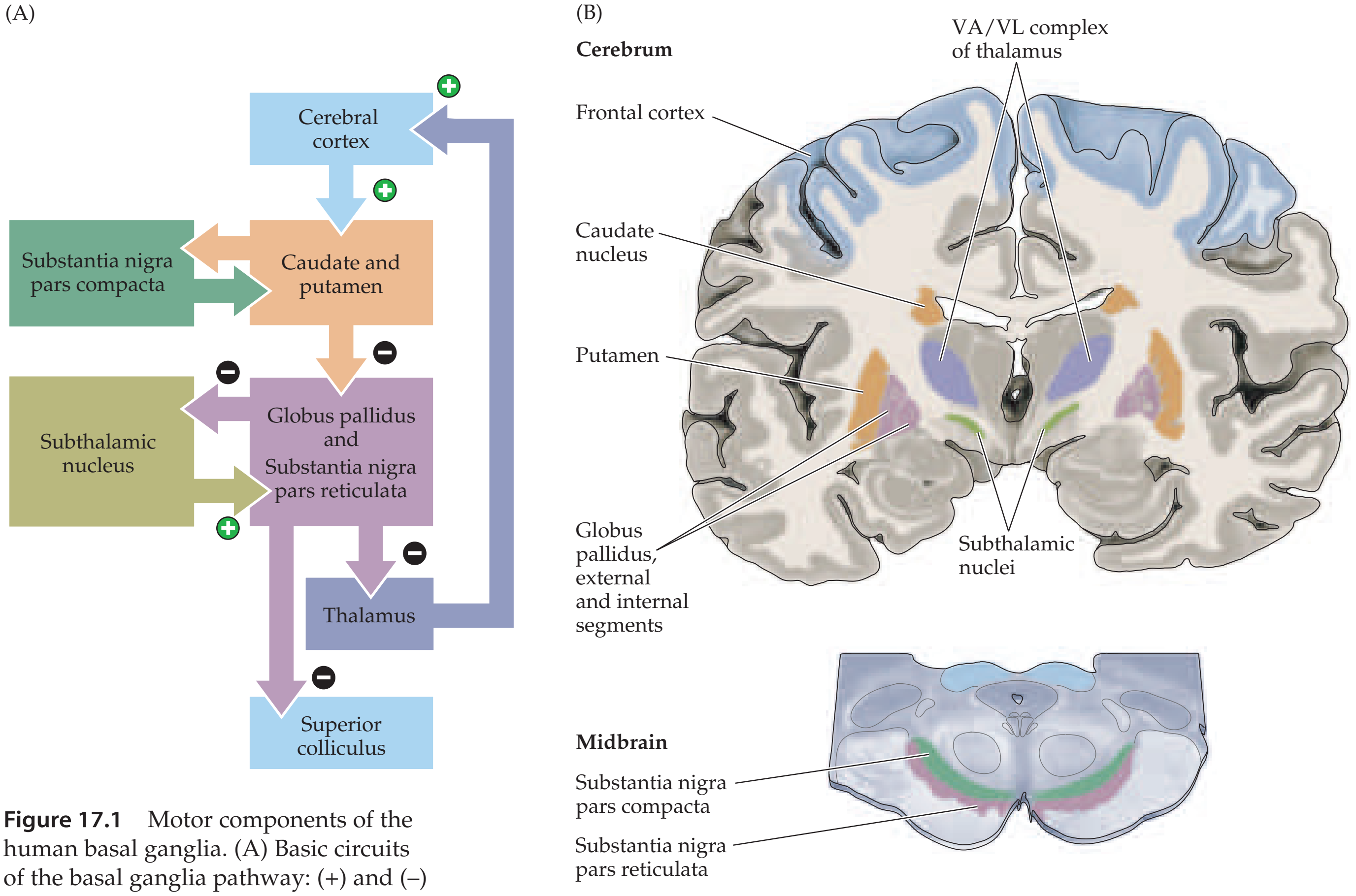

(A)
Cerebral cortex
Caudate and putamen
Substantia nigra pars compacta
Subthalamic nucleus
Globus pallidus and Substantia nigra pars reticulata
Thalamus
Superior colliculus
(B)
Cerebrum
VA/VL complex of thalamus
Frontal cortex
Caudate nucleus
Putamen
Globus pallidus, external and internal segments
Subthalamic nuclei
Midbrain
Substantia nigra pars compacta
Substantia nigra pars reticulata

Figure 17.1 Motor components of the human basal ganglia. (A) Basic circuits of the basal ganglia pathway: (+) and (–) denote excitory and inhibitory connections. (B) Idealized coronal section through the brain showing anatomical locations of structures involved in the basal ganglia pathway. Most of these structures are in the telencephalon, although the substantia nigra is in the midbrain and the thalamic and subthalamic nuclei are in the diencephalon. The ventral anterior and ventral lateral thalamic nuclei (VA/VL complex) are the targets of the basal ganglia, relaying the modulatory effects of the basal ganglia to upper motor neurons in the cortex.

cortex are the dendrites of a class of cells called **medium spiny neurons** in the corpus striatum (Figure 17.3). The large dendritic trees of these neurons allow them to integrate inputs from a variety of cortical, thalamic, and brainstem structures. The axons arising from the medium spiny neurons converge on neurons in the globus pallidus and the substantia nigra pars reticulata. The globus pallidus and substantia nigra pars reticulata are the main sources of *output* from the basal ganglia complex.

Nearly all regions of the neocortex project directly to the corpus striatum, making the cerebral cortex the source of the largest input to the basal ganglia by far. Indeed, the only cortical areas that do not project to the corpus striatum are the primary visual and primary auditory cortices (Figure 17.4). Of those cortical areas that do innervate the striatum, the heaviest projections are from association areas in the frontal and parietal lobes, but substantial contributions also arise from the temporal, insular, and cingulate cortices. All of these projections, referred to collectively as the **corticostriatal pathway**, travel through the internal capsule to reach the caudate and putamen directly (see Figure 17.2).

The cortical inputs to the caudate and putamen are not equivalent, however, and the differences in input reflect functional differences between these two nuclei. The caudate nucleus receives cortical projections primarily from multimodal association cortices, and from motor areas in the frontal lobe that control eye movements. As the name implies, the association cortices do not process any one type of sensory information; rather, they receive inputs from a number of primary and secondary sensory cortices and associated

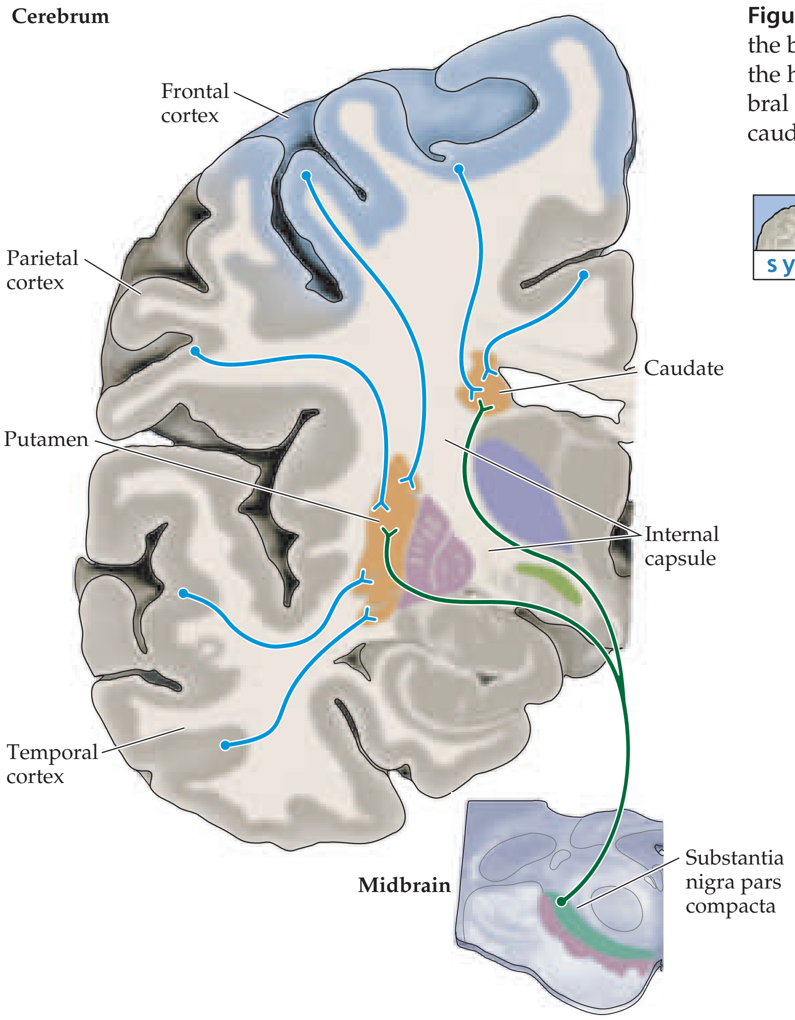


Figure 17.2 Anatomical organization of the inputs to the basal ganglia. An idealized coronal section through the human brain, showing the projections from the cerebral cortex and the substantia nigra pars comparta to the caudate and putamen.

thalamic nuclei (see Chapter 25). The putamen, on the other hand, receives input from the primary and secondary somatic sensory cortices in the parietal lobe, the secondary (extrastriate) visual cortices in the occipital and temporal lobes, the premotor and motor cortices in the frontal lobe, and the auditory association areas in the temporal lobe. The fact that different cortical areas project to different regions of the striatum implies that the corticostriatal pathway consists of multiple parallel pathways serving different functions. This interpretation is supported by the observation that the segregation is maintained in the structures that receive projections from the striatum, and in the pathways that project from the basal ganglia to other brain regions.

There are other indications that the corpus striatum is functionally subdivided according to its inputs. For example, visual and somatic sensory cortical projections are topographically mapped within different regions of the putamen. Moreover, the cortical areas that are functionally interconnected at the level of the cortex give rise to projections that overlap extensively in the striatum. Anatomical studies by Ann Graybiel and her colleagues at the Massachusetts Institute of Technology have shown that regions of different cortical areas concerned with the hand (see Chapter 8) converge in specific rostrocaudal bands within the striatum; conversely, regions in the same corti-

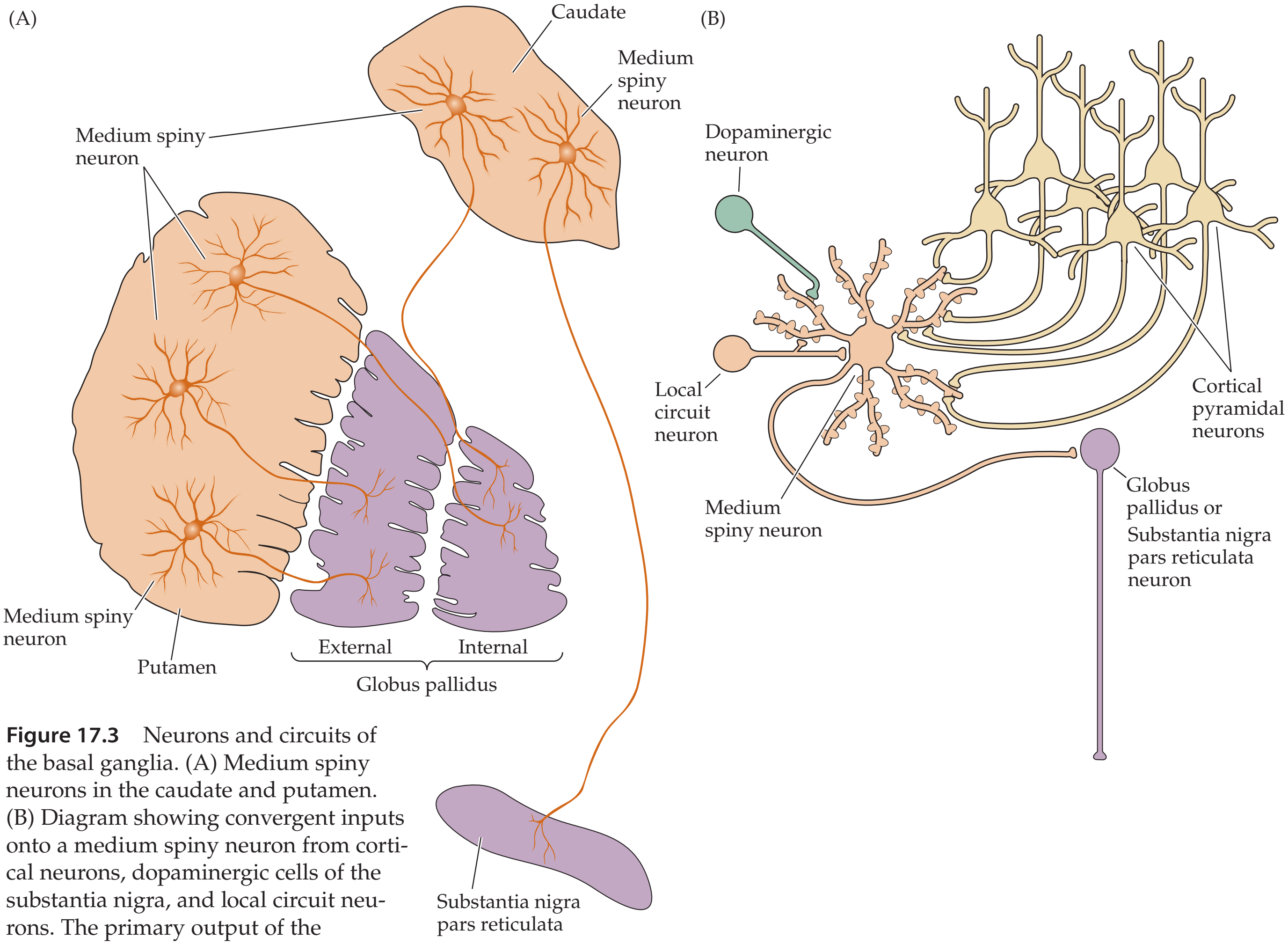

(A)
Caudate
Medium spiny neuron
Medium spiny neuron
Medium spiny neuron
Putamen
External
Internal
Globus pallidus
Substantia nigra pars reticulata
(B)
Dopaminergic neuron
Local circuit neuron
Medium spiny neuron
Cortical pyramidal neurons
Globus pallidus or Substantia nigra pars reticulata neuron

Figure 17.3 Neurons and circuits of the basal ganglia. (A) Medium spiny neurons in the caudate and putamen. (B) Diagram showing convergent inputs onto a medium spiny neuron from cortical neurons, dopaminergic cells of the substantia nigra, and local circuit neurons. The primary output of the medium spiny cells is to the globus pallidus and to the substantia nigra pars reticulata.

cal areas concerned with the leg converge in other striatal bands. These rostrocaudal bands therefore appear to be functional units concerned with the movement of particular body parts. Another study by the same group showed that the more extensively cortical areas are interconnected by corticocortical pathways, the greater the overlap in their projections to the striatum.

A further indication of functional subdivision within the striatum is the spatial distribution of different types of medium spiny neurons. Although medium spiny neurons are distributed throughout the striatum, they occur in clusters of cells called “patches” or “striosomes,” in a surrounding “matrix” of neurochemically distinct cells. Whereas the distinction between the patches and matrix was originally based only on differences in the types of neuropeptides contained by the medium spiny cells in the two regions, the cell types are now known to differ as well in the sources of their inputs from the cortex and in the destinations of their projections to other parts of the basal ganglia. For example, even though most cortical areas project to medium spiny neurons in both these compartments, limbic areas of the cortex (such as the cingulate gyrus; see Chapter 28) project more heavily to the patches, whereas motor and somatic sensory areas project preferentially to the neurons in the matrix. These differences in the connectivity of medium spiny neurons in the patches and matrix further support the conclusion that functionally distinct pathways project in parallel from the cortex to the striatum.

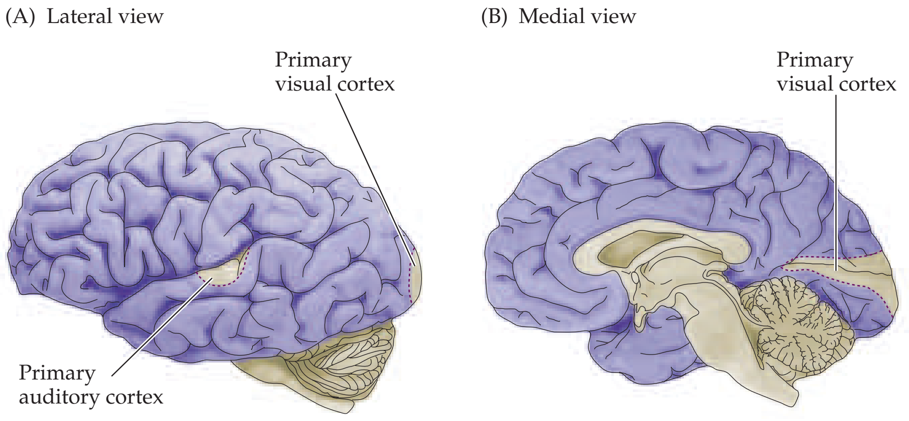


Figure 17.4 Regions of the cerebral cortex (shown in purple) that project to the caudate, putamen, and ventral striatum (see Box C) in both lateral (A) and medial (B) views. The caudate, putamen, and ventral striatum receive cortical projections primarily from the association areas of the frontal, parietal, and temporal lobes.

The nature of the signals transmitted to the caudate and putamen from the cortex is not understood. It is known, however, that collateral axons of corticocortical, corticothalamic, and corticospinal pathways all form excitatory glutamatergic synapses on the dendritic spines of medium spiny neurons (see Figure 17.3B). The arrangement of these cortical synapses is such that the number of contacts established between an individual cortical axon and a single medium spiny cell is very small, whereas the number of spiny neurons contacted by a single axon is extremely large. This divergence of axon terminals allows a single medium spiny neuron to integrate the influences of thousands of cortical cells.

The medium spiny cells also receive noncortical inputs from interneurons, from the midline and intralaminar nuclei of the thalamus, and from brainstem aminergic nuclei. In contrast to the cortical inputs to the dendritic spines, the local circuit neuron and thalamic synapses are made on the dendritic shafts and close to the cell soma, where they can modulate the effectiveness of cortical synaptic activation arriving from the more distal dendrites. The aminergic inputs are dopaminergic and they originate in a subdivision of the substantia nigra called **pars compacta** because of its densely packed cells. The dopaminergic synapses are located on the base of the spine, in close proximity to the cortical synapses, where they more directly modulate cortical input (see Figure 17.3B). As a result, inputs from both the cortex and the substantia nigra pars compacta are relatively far from the initial segment of the medium spiny neuron axon, where the nerve impulse is generated. Accordingly, the medium spiny neurons must simultaneously receive many excitatory inputs from cortical and nigral neurons to become active. As a result the medium spiny neurons are usually silent.

When the medium spiny neurons do become active, their firing is associated with the occurrence of a movement. Extracellular recordings show that these neurons typically increase their rate of discharge just before an impending movement. Neurons in the putamen tend to discharge in anticipation of body movements, whereas caudate neurons fire prior to eye movements. These anticipatory discharges are evidently part of a movement selection process; in fact, they can precede the initiation of movement by as much as several seconds. Similar recordings have also shown that the discharges of some striatal neurons vary according to the location in space of the *target* of a movement, rather than with the starting position of the limb relative to the target. Thus, the activity of these cells may encode the decision to move toward the target, rather than simply the direction and amplitude of the actual movement necessary to reach the target.

Projections from the Basal Ganglia to Other Brain Regions

The medium spiny neurons of the caudate and putamen give rise to inhibitory GABAergic projections that terminate in another pair of nuclei in the basal ganglia complex: the **internal division of the globus pallidus** and a specific region of the substantia nigra called **pars reticulata** (because, unlike the pars compacta, axons passing through give it a netlike appearance). These nuclei are in turn the major sources of the output from the basal ganglia (Figure 17.5). The globus pallidus and substantia nigra pars reticulata have similar output functions. In fact, developmental studies show that pars reticulata is actually part of the globus pallidus, although the two eventually become separated by fibers of the internal capsule. The striatal projections to these two nuclei resemble the corticostriatal pathways in that they terminate in rostrocaudal bands, the locations of which vary with the locations of their sources in the striatum.

A striking feature of the projections from the medium spiny neurons to the globus pallidus and substantia nigra is the degree of their convergence onto pallidal and reticulata cells. In humans, for example, the corpus striatum contains approximately 100 million neurons, about 75% of which are

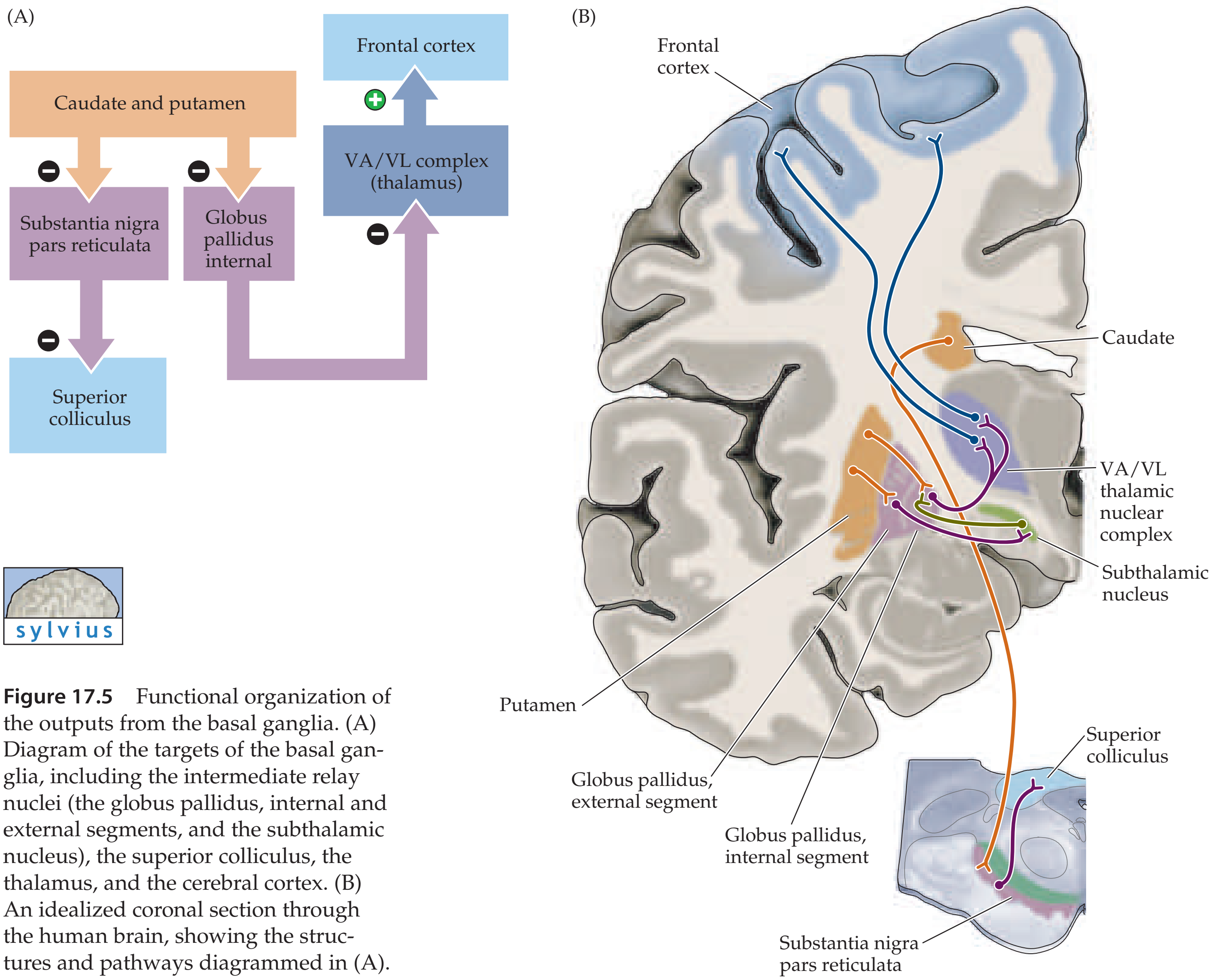

(A)
Frontal cortex
Caudate and putamen
+
VA/VL complex (thalamus)
−
−
Substantia nigra pars reticulata
Globus pallidus internal
−
−
Superior colliculus
(B)
Frontal cortex
Caudate
VA/VL thalamic nuclear complex
Subthalamic nucleus
Putamen
Globus pallidus, external segment
Globus pallidus, internal segment
Superior colliculus
Substantia nigra pars reticulata

Figure 17.5 Functional organization of the outputs from the basal ganglia. (A) Diagram of the targets of the basal ganglia, including the intermediate relay nuclei (the globus pallidus, internal and external segments, and the subthalamic nucleus), the superior colliculus, the thalamus, and the cerebral cortex. (B) An idealized coronal section through the human brain, showing the structures and pathways diagrammed in (A).

medium spiny neurons. In contrast, the main destination of their axons , the globus pallidus, comprises only about 700,000 cells. Thus, on average, more than 100 medium spiny neurons innervate each pallidal cell.

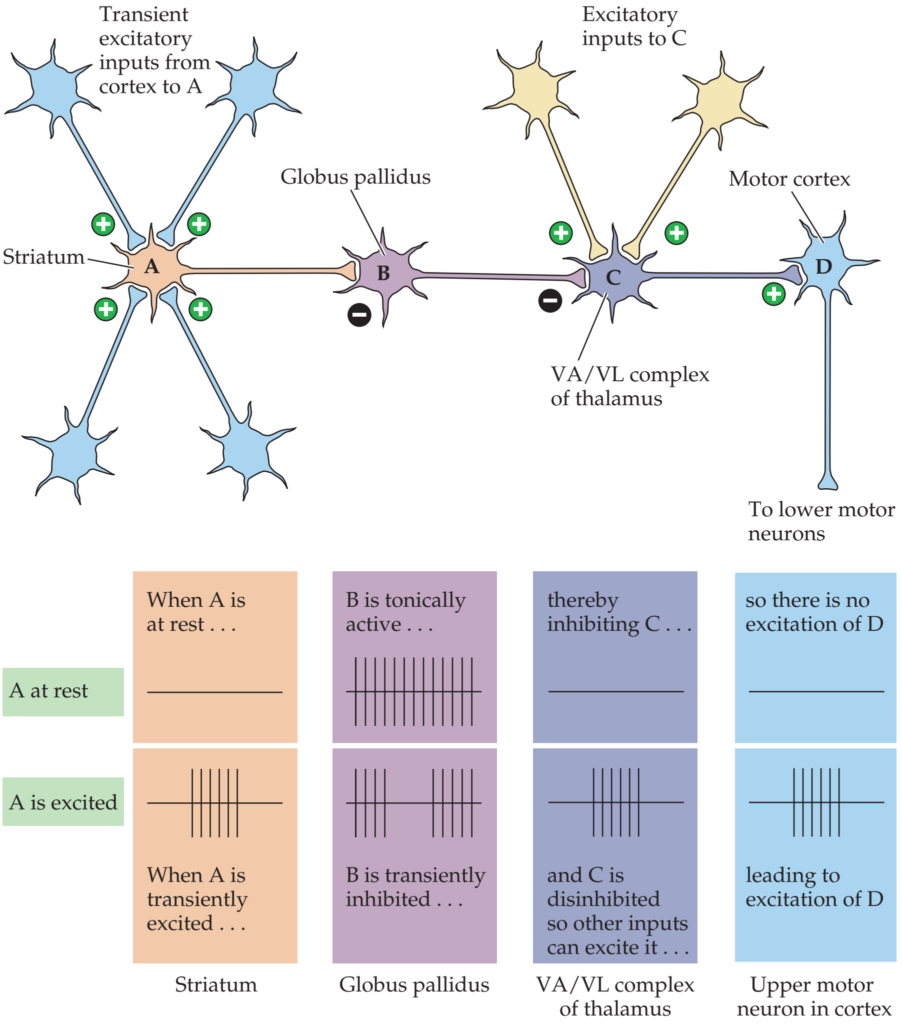
The efferent neurons of the internal globus pallidus and substantia nigra pars reticulata together give rise to the major pathways that link the basal ganglia with upper motor neurons located in the cortex and in the brainstem (see Figure 17.5). The pathway to the cortex arises primarily in the internal globus pallidus and reaches the motor cortex after a relay in the **ventral anterior** and **ventral lateral nuclei** of the dorsal thalamus. These thalamic nuclei project directly to motor areas of the cortex, thus completing a vast loop that originates in multiple cortical areas and terminates (after relays in the basal ganglia and thalamus) back in the motor areas of the frontal lobe. In contrast, the axons from substantia nigra pars reticulata synapse on upper motor neurons in the superior colliculus that command eye movements, without an intervening relay in the thalamus (see Figure 16.2 and Chapter 19). This difference between the globus pallidus and substantia nigra pars reticulata is not absolute, however, since many reticulata axons also project to the thalamus where they contact relay neurons that project to the frontal eye fields of the premotor cortex (see Chapter 19).

Because the efferent cells of both the globus pallidus and substantia nigra pars reticulata are GABAergic, the main output of the basal ganglia is *inhibitory*. In contrast to the quiescent medium spiny neurons, the neurons in both these output zones have high levels of spontaneous activity that tend to prevent unwanted movements by tonically inhibiting cells in the superior colliculus and thalamus. Since the medium spiny neurons of the striatum also are GABAergic and inhibitory, the net effect of the excitatory inputs that reach the striatum from the cortex is to inhibit the tonically active inhibitory cells of the globus pallidus and substantia nigra pars reticulata (Figure 17.6). Thus, in the absence of body movements, the globus pallidus neurons, for example, provide tonic inhibition to the relay cells in the ventral lateral and anterior nuclei of the thalamus. When the pallidal cells are inhibited by activity of the medium spiny neurons, the thalamic neurons are *disinhibited* and can relay signals from other sources to the upper motor neurons in the cortex. This **disinhibition** is what normally allows the upper motor neurons to send commands to local circuit and lower motor neurons that initiate movements. Conversely, an abnormal reduction in the tonic inhibition as a consequence of basal ganglia dysfunction leads to excessive excitability of the upper motor neurons, and thus to the involuntary movement syndromes that are characteristic of basal ganglia disorders such as **Huntington's disease** (Box A; see also Figure 17.9A).

Evidence from Studies of Eye Movements

The permissive role of the basal ganglia in the initiation of movement is perhaps most clearly demonstrated by studies of eye movements carried out by Okihide Hikosaka and Robert Wurtz at the National Institutes of Health (Figure 17.7). As described in the previous section, the substantia nigra pars reticulata is part of the output circuitry of the basal ganglia. Instead of projecting to the cortex, however, it sends axons mainly to the deep layers of the superior colliculus. The upper motor neurons in these layers command the rapid orienting movements of the eyes called *saccades* (see Chapter 19). When the eyes are not scanning the environment, these upper motor neurons are tonically inhibited by the spontaneously active reticulata cells to prevent unwanted saccades. Shortly before the onset of a saccade, the tonic

Figure 17.6 A chain of nerve cells arranged in a disinhibitory circuit. *Top:* Diagram of the connections between two inhibitory neurons, A and B, and an excitatory neuron, C. *Bottom:* Pattern of the action potential activity of cells A, B, and C when A is at rest, and when neuron A fires transiently as a result of its excitatory inputs. Such circuits are central to the gating operations of the basal ganglia.


Transient excitatory inputs from cortex to A
Excitatory inputs to C
Globus pallidus
Motor cortex
Striatum
A
B
C
D
VA/VL complex of thalamus
To lower motor neurons
A at rest
A is excited
When A is at rest . . .
B is tonically active . . .
thereby inhibiting C . . .
so there is no excitation of D
When A is transiently excited . . .
B is transiently inhibited . . .
and C is disinhibited so other inputs can excite it . . .
leading to excitation of D
Striatum
Globus pallidus
VA/VL complex of thalamus
Upper motor neuron in cortex

discharge rate of the reticulata neurons is sharply reduced by input from the GABAergic medium spiny neurons of the caudate, which have been activated by signals from the cortex. The subsequent reduction in the tonic discharge from reticulata neurons disinhibits the upper motor neurons of the superior colliculus, allowing them to generate the bursts of action potentials that command the saccade. Thus, the projections from substantia nigra pars reticulata to the upper motor neurons act as a physiological "gate" that must be "opened" to allow either sensory or other, more complicated, signals from cognitive centers to activate the upper motor neurons and initiate a saccade. Upper motor neurons in the cortex are similarly gated by the basal ganglia but, as discussed earlier, the tonic inhibition is mediated mainly by the GABAergic projection from the internal division of the globus pallidus to the relay cells in the ventral lateral and anterior nuclei of the thalamus (see Figures 17.5 and 17.6).

Circuits within the Basal Ganglia System

The projections from the medium spiny neurons of the caudate and putamen to the internal segment of the globus pallidus and substantia nigra pars

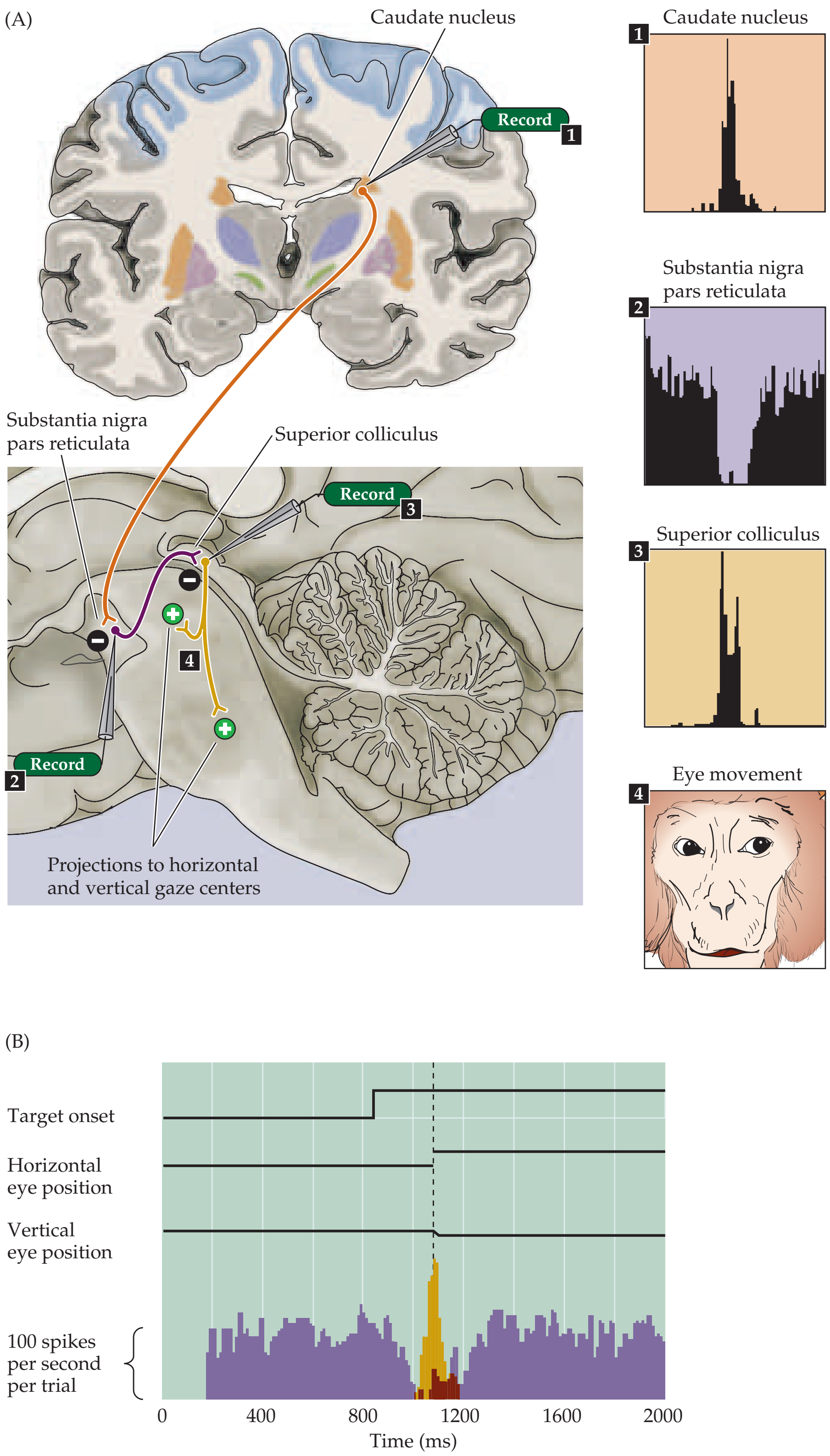

(A)
Caudate nucleus
Record
1
Substantia nigra
pars reticulata
Superior colliculus
Record
3
4
Record
2
Projections to horizontal
and vertical gaze centers
1
Caudate nucleus
Substantia nigra
pars reticulata
2
Superior colliculus
3
Eye movement
4
(B)
Target onset
Horizontal
eye position
Vertical
eye position
100 spikes
per second
per trial
0
400
800
1200
1600
2000
Time (ms)

Figure 17.7 The role of basal ganglia disinhibition in the generation of saccadic eye movements. (A) Medium spiny cells in the caudate nucleus respond with a transient burst of action potentials to an excitatory input from the cerebral cortex (1). The spiny cells inhibit the tonically active GABAergic cells in substantia nigra pars reticulata (2). As a result, the upper motor neurons in the deep layers of the superior colliculus are no longer tonically inhibited and can generate the bursts of action potentials that command a saccade (3, 4). (B) The temporal relationship between inhibition in substantia nigra pars reticulata (purple) and disinhibition in the superior colliculus (yellow) preceding a saccade to a visual target. (After Hikosaka and Wurtz, 1989.)

Box A

Huntington's Disease

In 1872, a physician named George Huntington described a group of patients seen by his father and grandfather in their practice in East Hampton, Long Island. The disease he defined, which became known as Huntington's disease (HD), is characterized by the gradual onset of defects in behavior, cognition, and movement beginning in the fourth and fifth decades of life. The disorder is inexorably progressive, resulting in death within 10 to 20 years. HD is inherited in an autosomal dominant pattern, a feature that has led to a much better understanding of its cause in molecular terms.

One of the more common inherited neurodegenerative diseases, HD usually presents as an alteration in mood (especially depression) or a change in personality that often takes the form of increased irritability, suspiciousness, and impulsive or eccentric behavior. Defects of memory and attention may also occur. The hallmark of the disease, however, is a movement disorder consisting of rapid, jerky motions with no clear purpose; these choreiform movements may be confined to a finger or may involve a whole extremity, the facial musculature, or even the vocal apparatus. The movements themselves are involuntary, but the patient often incorporates them into apparently deliberate actions, presumably in an effort to obscure the problem. There is no weakness, ataxia, or deficit of sensory function. Occasionally, the disease begins in childhood or adolescence. The clinical manifestations in juveniles include rigidity, seizures, more marked dementia, and a rapidly progressive course.

A distinctive neuropathology is associated with these clinical manifestations: a profound but selective atrophy of the caudate and putamen, with some associated degeneration of the frontal and temporal cortices (see Figure 17.9A). This pattern of destruction is thought to explain the disorders of movement, cognition, and behavior, as well as the sparing of other neurological functions.

The availability of extensive HD pedigrees has allowed geneticists to decipher the molecular cause of this disease. HD was one of the first human diseases in which DNA polymorphisms were used to localize the mutant gene, which in 1983 was mapped to the short arm of chromosome 4. This discovery led to an intensive effort to identify the HD gene within this region by positional cloning. Ten years later, these efforts culminated in identification of the gene (named *Huntingtin*) responsible for the disease. In contrast to previously recognized forms of mutations such as point mutations, deletions, or insertions, the mutation of *Huntingtin* is an unstable triplet repeat. In normal individuals, *Huntingtin* contains between 15 and 34 repeats, whereas the gene in HD patients contains from 42 to over 66 repeats.

HD is one of a growing number of diseases attributed to unstable DNA segments. Other examples are fragile X syndrome, myotonic dystrophy, spinal and bulbar muscular atrophy, and spinocerebellar ataxia type 1. In the latter two and HD, the repeats consist of a DNA segment (CAG) that codes for the amino acid glutamine and is present within the coding region of the gene.

The mechanism by which the increased number of polyglutamine repeats injures neurons is not clear. The leading hypothesis is that the increased numbers of glutamines alter protein folding, which somehow triggers a cascade of molecular events culminating in dysfunction and neuronal death. Interestingly, although *Huntingtin* is expressed predominantly in the expected neurons in the basal ganglia, it is also present in regions of the brain that are not affected in HD. Indeed, the gene is expressed in many organs outside the nervous system. How and why the mutant *Huntingtin* uniquely injures striatal neurons is unclear. Continuing to elucidate this molecular pathogenesis will no doubt provide further insight into this and other triplet repeat diseases.

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reticulata are part of a "direct pathway" and, as just described, serve to release the upper motor neurons from tonic inhibition. This pathway is summarized in Figure 17.8A. A second pathway serves to increase the level of tonic inhibition and is called the "indirect pathway" (Figure 17.8B). This pathway provides a second route, linking the corpus striatum with the inter-

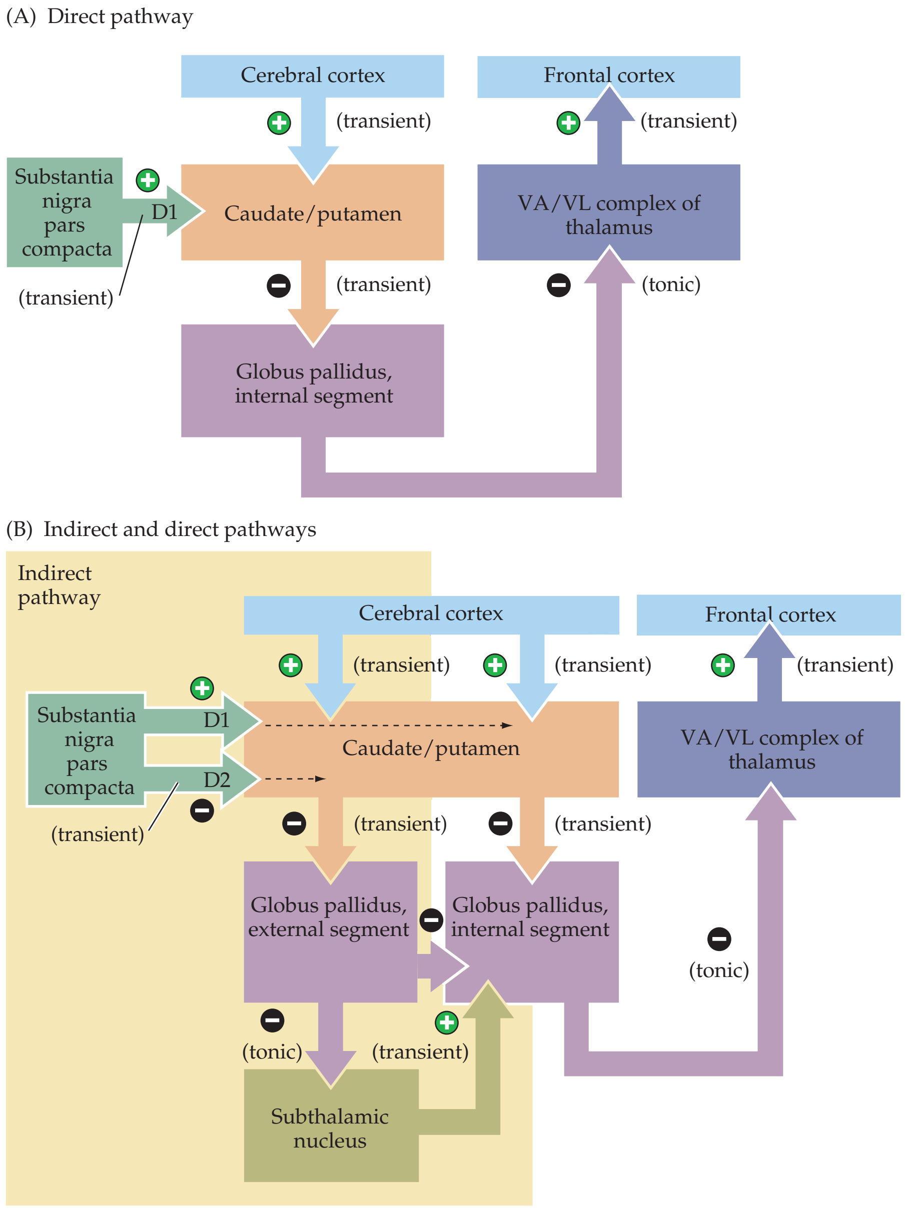

(A) Direct pathway
Cerebral cortex
Frontal cortex
(transient)
(transient)
Substantia nigra pars compacta
D1
Caudate/putamen
VA/VL complex of thalamus
(transient)
(transient)
(tonic)
Globus pallidus, internal segment
(B) Indirect and direct pathways
Indirect pathway
Cerebral cortex
Frontal cortex
(transient)
(transient)
(transient)
Substantia nigra pars compacta
D1
D2
Caudate/putamen
VA/VL complex of thalamus
(transient)
(transient)
(transient)
Globus pallidus, external segment
Globus pallidus, internal segment
(tonic)
(tonic)
(transient)
Subthalamic nucleus

Figure 17.8 Disinhibition in the direct and indirect pathways through the basal ganglia. (A) In the direct pathway, transiently inhibitory projections from the caudate and putamen project to tonically active inhibitory neurons in the *internal* segment of the globus pallidus, which project in turn to the VA/VL complex of the thalamus. Transiently excitatory inputs to the caudate and putamen from the cortex and substantia nigra are also shown, as is the transiently excitatory input from the thalamus back to the cortex. (B) In the indirect pathway (shaded yellow), transiently active inhibitory neurons from the caudate and putamen project to tonically active inhibitory neurons of the *external* segment of the globus pallidus. Note that the influence of nigral dopaminergic input to neurons in the indirect pathway is inhibitory. The globus pallidus (external segment) neurons project to the subthalamic nucleus, which also receives a strong excitatory input from the cortex. The subthalamic nucleus in turn projects to the globus pallidus (internal segment), where its transiently excitatory drive acts to oppose the disinhibitory action of the direct pathway. In this way, the indirect pathway modulates the effects of the direct pathway.

nal globus pallidus and substantia nigra pars reticulata. In the indirect pathway, a population of medium spiny neurons projects to the lateral or **external segment of the globus pallidus**. This external division sends projections both to the internal segment of the globus pallidus and to the **subthalamic nucleus** of the ventral thalamus (see Figure 17.1). But, instead of projecting to structures *outside* of the basal ganglia, the subthalamic nucleus projects back to the internal segment of the globus pallidus and to the substantia nigra pars reticulata. As already described, these latter two nuclei project out of the basal ganglia, which thus allows the indirect pathway to influence the activity of the upper motor neurons.

The indirect pathway through the basal ganglia apparently serves to modulate the disinhibitory actions of the direct pathway. The subthalamic nucleus neurons that project to the internal globus pallidus and substantia nigra pars reticulata are excitatory. Normally, when the indirect pathway is activated by signals from the cortex, the medium spiny neurons discharge and inhibit the tonically active GABAergic neurons of the external globus pallidus. As a result, the subthalamic cells become more active and, by virtue of their excitatory synapses with cells of the internal globus pallidus and reticulata, they increase the inhibitory outflow of the basal ganglia. Thus, in contrast to the direct pathway, which when activated reduces tonic inhibition, the net effect of activity in the indirect pathway is to increase inhibitory influences on the upper motor neurons. The indirect pathway can thus be regarded as a "brake" on the normal function of the direct pathway. Indeed, many neural systems achieve fine control of their output by a similar interplay between excitation and inhibition.

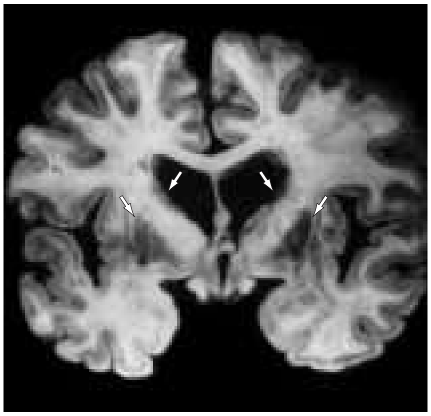
The consequences of imbalances in this fine control mechanism are apparent in diseases that affect the subthalamic nucleus. These disorders remove a source of excitatory input to the internal globus pallidus and reticulata, and thus abnormally reduce the inhibitory outflow of the basal ganglia. A basal ganglia syndrome called **hemiballismus**, which is characterized by violent, involuntary movements of the limbs, is the result of damage to the subthalamic nucleus. The involuntary movements are initiated by abnormal discharges of upper motor neurons that are receiving less tonic inhibition from the basal ganglia.

Another circuit within the basal ganglia system entails the dopaminergic cells in the pars compacta subdivision of substantia nigra and modulates the output of the corpus striatum. The medium spiny neurons of the corpus striatum project directly to substantia nigra pars compacta, which in turn sends widespread dopaminergic projections back to the spiny neurons. These dopaminergic influences on the spiny neurons are complex: The same nigral neurons can provide excitatory inputs mediated by D1 type dopaminergic receptors on the spiny cells that project to the internal globus pallidus (the direct pathway), and inhibitory inputs mediated by D2 type receptors on the spiny cells that project to the external globus pallidus (the indirect pathway). Since the actions of the direct and indirect pathways on the output of the basal ganglia are antagonistic, these different influences of the nigrostriatal axons produce the same effect, namely a decrease in the inhibitory outflow of the basal ganglia.

The modulatory influences of this second internal circuit help explain many of the manifestations of basal ganglia disorders. For example, **Parkinson's disease** is caused by the loss of the nigrostriatal dopaminergic neurons (Figure 17.9B and Box B). As mentioned earlier, the normal effects of the compacta input to the striatum are *excitation* of the medium spiny neurons that project directly to the internal globus pallidus and *inhibition* of the spiny neurons that project to the external globus pallidus cells in the indirect pathway. Normally, both of these dopaminergic effects serve to decrease the inhibitory outflow of the basal ganglia and thus to increase the excitability of the upper motor neurons (Figure 17.10A). In contrast, when the compacta cells are destroyed, as occurs in Parkinson's disease, the inhibitory outflow of the basal ganglia is abnormally high, and thalamic activation of upper motor neurons in the motor cortex is therefore less likely to occur.

In fact, many of the symptoms seen in Parkinson's disease (and in other *hypokinetic* movement disorders) reflect a failure of the disinhibition normally mediated by the basal ganglia. Thus, Parkinsonian patients tend to have diminished facial expressions and lack "associated movements" such as arm swinging during walking. Indeed, any movement is difficult to initiate and, once initiated, is often difficult to terminate. Disruption of the same

(A) Huntington's disease



(B) Parkinson's disease

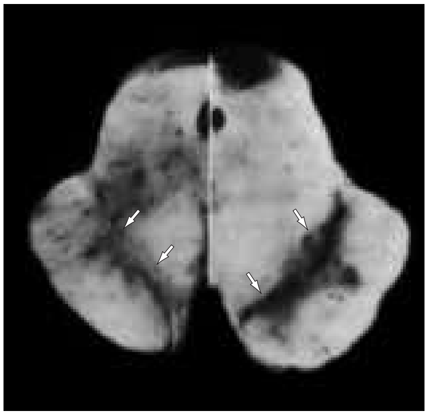


Figure 17.9 The pathological changes in certain neurological diseases provide insights about the function of the basal ganglia. (A) The size of the caudate and putamen (the striatum) (arrows) is dramatically reduced in patients with Huntington's disease. (B) *Left:* The midbrain from a patient with Parkinson's disease. The substantia nigra (pigmented area) is largely absent in the region above the cerebral peduncles (arrows). *Right:* The mesencephalon from a normal subject, showing intact substantia nigra (arrows). (From Bradley et al., 1991.)

Box B

Parkinson's Disease: An Opportunity for Novel Therapeutic Approaches

Parkinson's disease is the second most common degenerative disease of the nervous system (Alzheimer's disease being the leader; see Chapter 30). Described by James Parkinson in 1817, this disorder is characterized by tremor at rest, slowness of movement (bradykinesia), rigidity of the extremities and neck, and minimal facial expressions. Walking entails short steps, stooped posture, and a paucity of associated movements such as arm swinging. To make matters worse, in some patients these abnormalities of motor function are associated with dementia. Following a gradual onset between the ages of 50 and 70, the disease progresses slowly and culminates in death 10 to 20 years later.

The defects in motor function are due to the progressive loss of dopaminergic neurons in the substantia nigra pars compacta, a population that projects to and innervates neurons in the caudate and putamen (see text). Although the cause of the progressive deterioration of these dopaminergic neurons is not known, genetic investigations are providing clues to the etiology and pathogenesis. Whereas the majority of cases of Parkinson's disease are sporadic, there may be specific forms of susceptibility genes that confer increased risk of acquiring the disease, just as the *apoE4* allele increases the risk of Alzheimer's disease. Familial forms of the disease caused by single gene mutations account for less than 10% of all cases, However, identification of these rare genes is likely give some insight into molecular pathways that may underlie the disease. Mutations of three distinct genes—*α-synuclein*, *Parkin*, and *DJ-1*—have been implicated in rare forms of this disease. Identification of these genes provides an opportunity to generate mutant mice carrying the mutant form of the human gene, potentially providing a useful animal model in which the pathogenesis can be elucidated and therapies can be tested.

In contrast to other neurodegenerative diseases, such as Alzheimer's disease or amyotrophic lateral sclerosis, in Parkinson's disease the spatial distribution of the degenerating neurons is largely restricted to the substantia nigra pars compacta. This spatial restriction, combined with the defined and relatively homogeneous phenotype of the degenerating neurons (i. e., dopaminergic neurons), has provided an opportunity for novel therapeutic approaches to this disorder.

One strategy is so-called gene therapy. *Gene therapy* refers to the correction of a disease phenotype through the introduction of new genetic information into the affected organism. Although still in its infancy, this approach promises to revolutionize treatment of human disease. One therapy for Parkinson's disease would be to enhance release of dopamine in the caudate and putamen. In principle, this could be accomplished by implanting cells genetically modified to express tyrosine hydroxylase, the enzyme that converts tyrosine to L-DOPA, which in turn is converted by a nearly ubiquitous decarboxylase into the neurotransmitter dopamine. The feasibility of this approach has been demonstrated by transplanting tissue derived from the midbrain of human fetuses into the caudate and putamen, which produces long-lasting symptomatic improvement in a majority of grafted Parkinson's patients. (The fetal midbrain is enriched in developing neurons that express tyrosine hyroxylase and synthesize and release dopamine.) To date, however, ethical, practical, and political considerations have limited use of fetal transplanted tissue. The effects of transplanting non-neuronal cells genetically modified in vitro to express tyrosine hydroxylase are also being studied in patients with Parkinson's disease, an approach that avoids some of these problems.

An alternative strategy to treating Parkinsonian patients involves "neural grafts" using stem cells. Stem cells are self-renewing, multipotent progenitors with broad developmental potential (see Chapters 21 and 24). Instead of isolating mature dopaminergic neurons from the fetal midbrain for transplantation, this approach isolates neuronal progenitors at earlier stages of development, when these cells are actively proliferating. Critical to this approach is to prospectively identify and isolate stem cells that are multipotent and self-renewing, and to identify the growth factors needed to promote differentiation into the desired phenotype (e.g., dopaminergic neurons). The prospective identification and isolation of multipotent mammalian stem cells has already been accomplished, and several factors likely to be important in differentiation of midbrain precursors into dopamine neurons have been identified. Establishing the efficacy of this approach for Parkinson's patients would increase the possibility of its application to other neurodegenerative diseases.

Although therapeutic strategies like these remain experimental, it is likely that some of them will succeed.

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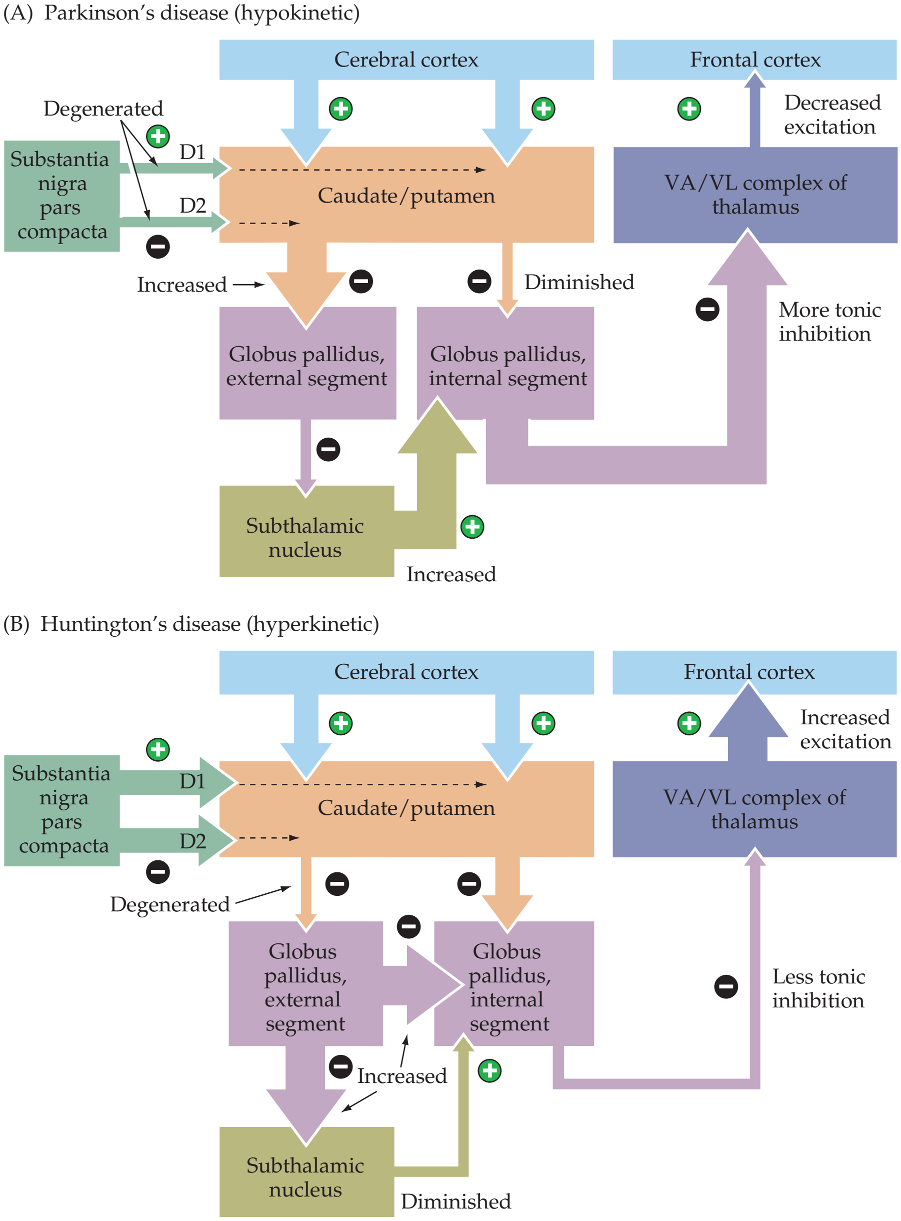
circuits also increases the discharge rate of the inhibitory cells in substantia nigra pars reticulata. The resulting increase in tonic inhibition reduces the excitability of the upper motor neurons in the superior colliculus and causes saccades to be reduced in both frequency and amplitude.

Support for this explanation of hypokinetic movement disorders like Parkinson's disease comes from studies of monkeys in which degeneration of the dopaminergic cells of substantia nigra has been induced by the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Monkeys (or humans) exposed to MPTP develop symptoms that are very similar to those of patients with Parkinson's disease. Furthermore, a second lesion placed in the subthalamic nucleus results in significant improvement in the ability of these animals to initiate movements, as would be expected based on the circuitry of the indirect pathway (see Figure 17.8B).


(A) Parkinson's disease (hypokinetic)
Cerebral cortex
Frontal cortex
Degenerated
Decreased excitation
Substantia nigra pars compacta
D1
D2
Caudate/putamen
VA/VL complex of thalamus
Increased
Diminished
More tonic inhibition
Globus pallidus, external segment
Globus pallidus, internal segment
Subthalamic nucleus
Increased
(B) Huntington's disease (hyperkinetic)
Cerebral cortex
Frontal cortex
Increased excitation
Substantia nigra pars compacta
D1
D2
Caudate/putamen
VA/VL complex of thalamus
Degenerated
Globus pallidus, external segment
Globus pallidus, internal segment
Less tonic inhibition
Increased
Subthalamic nucleus
Diminished

sylvius

Figure 17.10 Summary explanation of hypokinetic disorders such as Parkinson's disease and hyperkinetic disorders like Huntington's disease. In both cases, the balance of inhibitory signals in the direct and indirect pathways is altered, leading to a diminished ability of the basal ganglia to control the thalamic output to the cortex. (A) In Parkinson's disease, the inputs provided by the substantia nigra are diminished (thinner arrow), making it more difficult to generate the transient inhibition from the caudate and putamen. The result of this change in the direct pathway is to sustain the tonic inhibition from the globus pallidus (internal segment) to the thalamus, making thalamic excitation of the motor cortex less likely (thinner arrow from thalamus to cortex). (B) In hyperkinetic diseases such as Huntington's, the projection from the caudate and putamen to the globus pallidus (external segment) is diminished (thinner arrow). This effect increases the tonic inhibition from the globus pallidus to the subthalamic nucleus (larger arrow), making the excitatory subthalamic nucleus less effective in opposing the action of the direct pathway (thinner arrow). Thus, thalamic excitation of the cortex is increased (larger arrow), leading to greater and often inappropriate motor activity. (After DeLong, 1990.)

Similarly, knowledge about the indirect pathway within the basal ganglia helps explain the motor abnormalities seen in Huntington's disease (see Box A). In patients with Huntington's disease, medium spiny neurons that project to the external segment of the globus pallidus degenerate (see Figure 17.9A). In the absence of their normal inhibitory input from the spiny neurons, the external globus pallidus cells become abnormally active; this activity reduces in turn the excitatory output of the subthalamic nucleus to the internal globus pallidus (Figure 17.10B). In consequence, the inhibitory outflow of the basal ganglia is reduced. Without the restraining influence of the basal ganglia, upper motor neurons can be activated by inappropriate signals, resulting in the undesired ballistic and choreic (dancelike) movements that characterize Huntington's disease. Importantly, the basal ganglia may exert a similar influence on other *non-motor* systems with equally significant clinical implications (Box C).

As predicted by this account, GABA agonists and antagonists applied to substantia nigra pars reticulata of monkeys produce symptoms similar to those seen in human basal ganglia disease. For example, intranigral injection of bicuculline, which blocks the GABAergic inputs from the striatal medium spiny neurons to the reticulata cells, increases the amount of tonic inhibition on the upper motor neurons in the deep collicular layers. These animals exhibit fewer, slower saccades, reminiscent of patients with Parkinson's disease. In contrast, injections of the GABA agonist muscimol into substantia nigra pars reticulata decrease the tonic GABAergic inhibition of the upper motor neurons in the superior colliculus, with the result that the injected monkeys generate spontaneous, irrepressible saccades that resemble the involuntary movements characteristic of basal ganglia diseases such as hemiballismus and Huntington's disease (Figure 17.11).

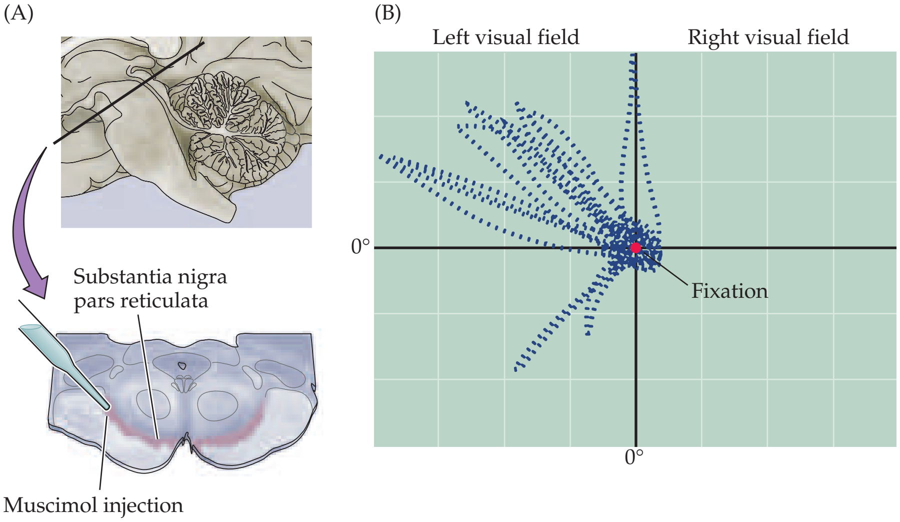


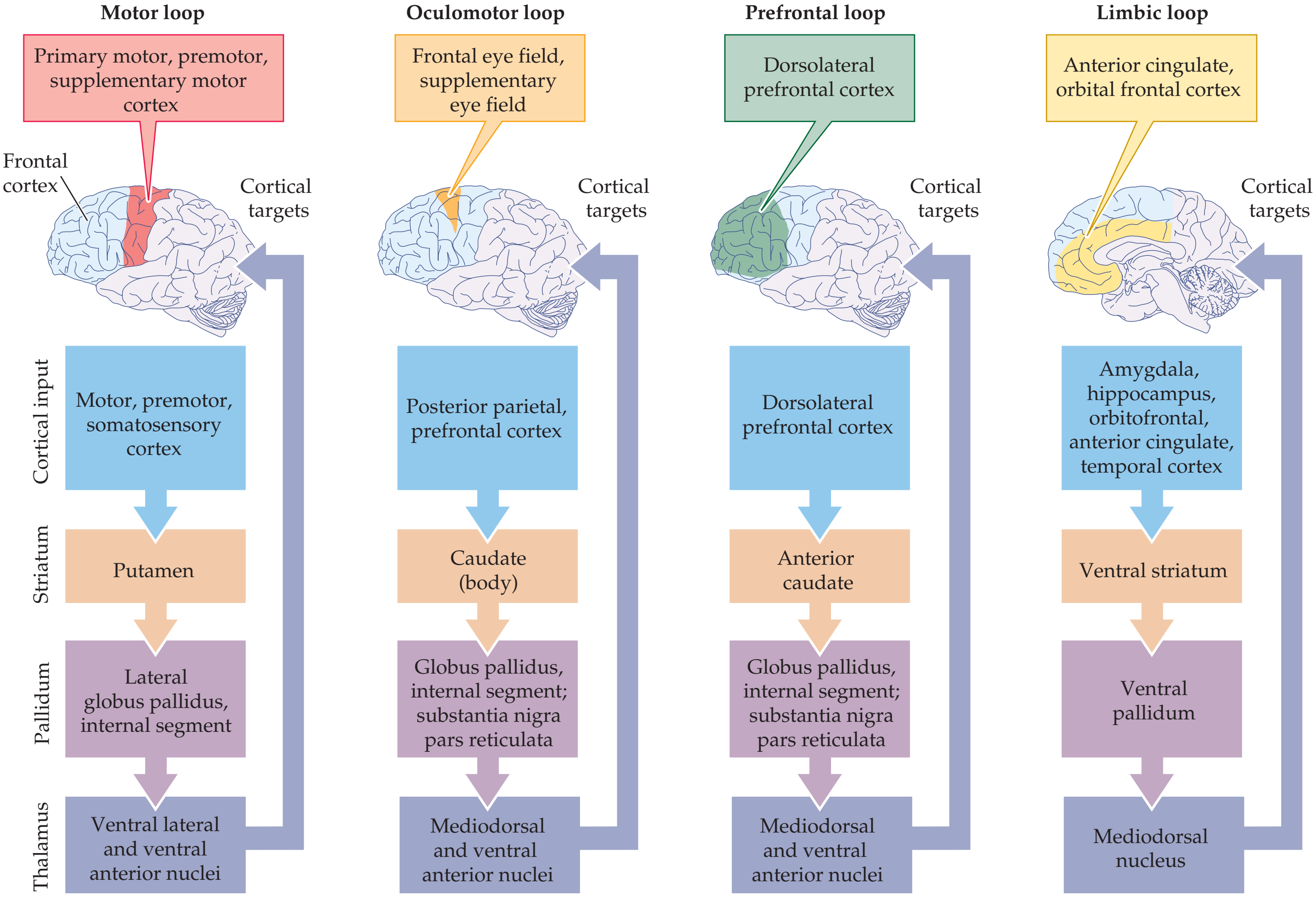
Figure 17.11 After the tonically active cells of substantia nigra pars reticulata are inactivated by an intranigral injection of muscimol (A), the upper motor neurons in the deep layers of the superior colliculus are disinhibited and the monkey generates spontaneous irrepressible saccades (B). The cells in both substantia nigra pars reticulata and the deep layers of the superior colliculus are arranged in spatially organized motor maps of saccade vectors (see Chapter 19), and so the direction of the involuntary saccades—in this case toward the upper left quadrant of the visual field—depends on the precise location of the injection site in the substantia nigra.

Box C

Basal Ganglia Loops and Non-Motor Brain Functions

Traditionally, the basal ganglia have been regarded as motor structures that regulate the initiation of movements. However, the basal ganglia are also central structures in anatomical circuits or loops that are involved in modulating non-motor aspects of behavior. These parallel loops originate in broad regions of the cortex, engage specific subdivisions of the basal ganglia and thalamus, and ultimately terminate in areas of the frontal lobe outside of the primary motor and premotor cortices. These non-motor loops (see figure) include a "prefrontal" loop involving the dorsolateral prefrontal cortex and part of the caudate (see Chapter 25), a "limbic" loop involving the cingulate cortex and the ventral striatum (see Chapter 28), and an "oculomotor" loop that modulates the activity of the frontal eye fields (see Chapter 19).

The anatomical similarity of these loops to the traditional motor loop suggests that the non-motor regulatory functions of the basal ganglia may be generally the same as what the basal ganglia do in regulating the initiation of movement. For example, the prefrontal loop may regulate the initiation and termination of cognitive processes such as planning, working memory, and attention. By the same token, the limbic loop may regulate emotional behavior and motivation. Indeed, the deterioration of cognitive and emotional function in both Huntington's disease (see Box A) and Parkinson's disease (see Box B) could be the result of disruption of these non-motor loops.


Motor loop
Primary motor, premotor, supplementary motor cortex
Frontal cortex
Cortical targets
Oculomotor loop
Frontal eye field, supplementary eye field
Cortical targets
Prefrontal loop
Dorsolateral prefrontal cortex
Cortical targets
Limbic loop
Anterior cingulate, orbital frontal cortex
Cortical targets
Cortical input
Striatum
Pallidum
Thalamus
Motor, premotor, somatosensory cortex
Putamen
Lateral globus pallidus, internal segment
Ventral lateral and ventral anterior nuclei
Posterior parietal, prefrontal cortex
Caudate (body)
Globus pallidus, internal segment; substantia nigra pars reticulata
Mediodorsal and ventral anterior nuclei
Dorsolateral prefrontal cortex
Anterior caudate
Globus pallidus, internal segment; substantia nigra pars reticulata
Mediodorsal and ventral anterior nuclei
Amygdala, hippocampus, orbitofrontal, anterior cingulate, temporal cortex
Ventral striatum
Ventral pallidum
Mediodorsal nucleus

sylvius

Comparison of the motor and three non-motor basal ganglia loops.

In fact, a variety of other disorders are now thought to be caused, at least in part, by damage to non-motor components of the basal ganglia. For example, patients with Tourette's syndrome produce inappropriate utterances and obscenities as well as unwanted vocal-motor "tics" and repetitive grunts. These manifestations may be a result of excessive activity in basal ganglia loops that regulate the cognitive circuitry of the prefrontal speech areas. Another example is schizophrenia, which some investigators have argued is associated with aberrant activity within the limbic and prefrontal loops, resulting in hallucinations, delusions, disordered thoughts, and loss of emotional expression. In support of the argument for a basal ganglia contribution to schizophrenia, antipsychotic drugs are known to act on dopaminergic receptors, which are found in high concentrations in the striatum. Still other psychiatric disorders, including obsessive-compulsive disorder, depression, and chronic anxiety, may also involve dysfunctions of the limbic loop. A challenge for future research is therefore to understand more fully the relationships between the clinical problems and other largely unexplored functions of the basal ganglia.

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Summary

The contribution of the basal ganglia to motor control is apparent from the deficits that result from damage to the component nuclei. Such lesions compromise the initiation and performance of voluntary movements, as exemplified by the paucity of movement in Parkinson's disease and in the inappropriate "release" of movements in Huntington's disease. The organization of the basic circuitry of the basal ganglia indicates how this constellation of nuclei modulates movement. With respect to motor function, the system forms a loop that originates in almost every area of the cerebral cortex and eventually terminates, after enormous convergence within the basal ganglia, on the upper motor neurons in the motor and premotor areas of the frontal lobe and in the superior colliculus. The efferent neurons of the basal ganglia influence the upper motor neurons in the cortex by gating the flow of information through relays in the ventral nuclei of the thalamus. The upper motor neurons in the superior colliculus that initiate saccadic eye movements are controlled by monosynaptic projections from substantia nigra pars reticulata. In each case, the basal ganglia loop regulates movement by a process of disinhibition that results from the serial interaction within the basal ganglia circuitry of two GABAergic neurons. Internal circuits within the basal ganglia system modulate the amplification of the signals that are transmitted through the loop.

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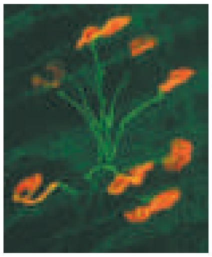
Chapter 18



Modulation of Movement by the Cerebellum

Overview

In contrast to the upper motor neurons described in Chapter 16, the efferent cells of the cerebellum do not project directly either to the local circuits of the brainstem and spinal cord that organize movement, or to the lower motor neurons that innervate muscles. Instead—like the basal ganglia—the cerebellum influences movements by modifying the activity patterns of the upper motor neurons. In fact, the cerebellum sends prominent projections to virtually all upper motor neurons. Structurally, the cerebellum has two main components: a laminated cerebellar cortex, and a subcortical cluster of cells referred to collectively as the deep cerebellar nuclei. Pathways that reach the cerebellum from other brain regions (in humans, predominantly the cerebral cortex) project to both components; thus, the afferent axons send branches to both the deep nuclei and the cerebellar cortex. The output cells of the cerebellar cortex project to the deep cerebellar nuclei, which give rise to the main efferent pathways that leave the cerebellum to regulate upper motor neurons in the cerebral cortex and brainstem. Thus, much like the basal ganglia, the cerebellum is part of a vast loop that receives projections from and sends projections back to the cerebral cortex and brainstem. The primary function of the cerebellum is evidently to detect the difference, or "motor error," between an intended movement and the actual movement, and, through its projections to the upper motor neurons, to reduce the error. These corrections can be made both during the course of the movement and as a form of motor learning when the correction is stored. When this feedback loop is damaged, as occurs in many cerebellar diseases, the afflicted individuals make persistent movement errors whose specific character depends on the location of the damage.

Organization of the Cerebellum

The **cerebellum** can be subdivided into three main parts based on differences in their sources of input (Figure 18.1; Table 18.1). By far the largest subdivision in humans is the **cerebrocerebellum**. It occupies most of the lateral cerebellar hemisphere and receives input from many areas of the cerebral cortex. This region of the cerebellum is especially well developed in primates. The cerebrocerebellum is concerned with the regulation of highly skilled movements, especially the planning and execution of complex spatial and temporal sequences of movement (including speech). The phylogenetically oldest part of the cerebellum is the **vestibulocerebellum**. This portion comprises the caudal lobes of the cerebellum and includes the **flocculus** and the **nodulus.** As its name suggests, the vestibulocerebellum receives input from the vestibular nuclei in the brainstem and is primarily concerned with

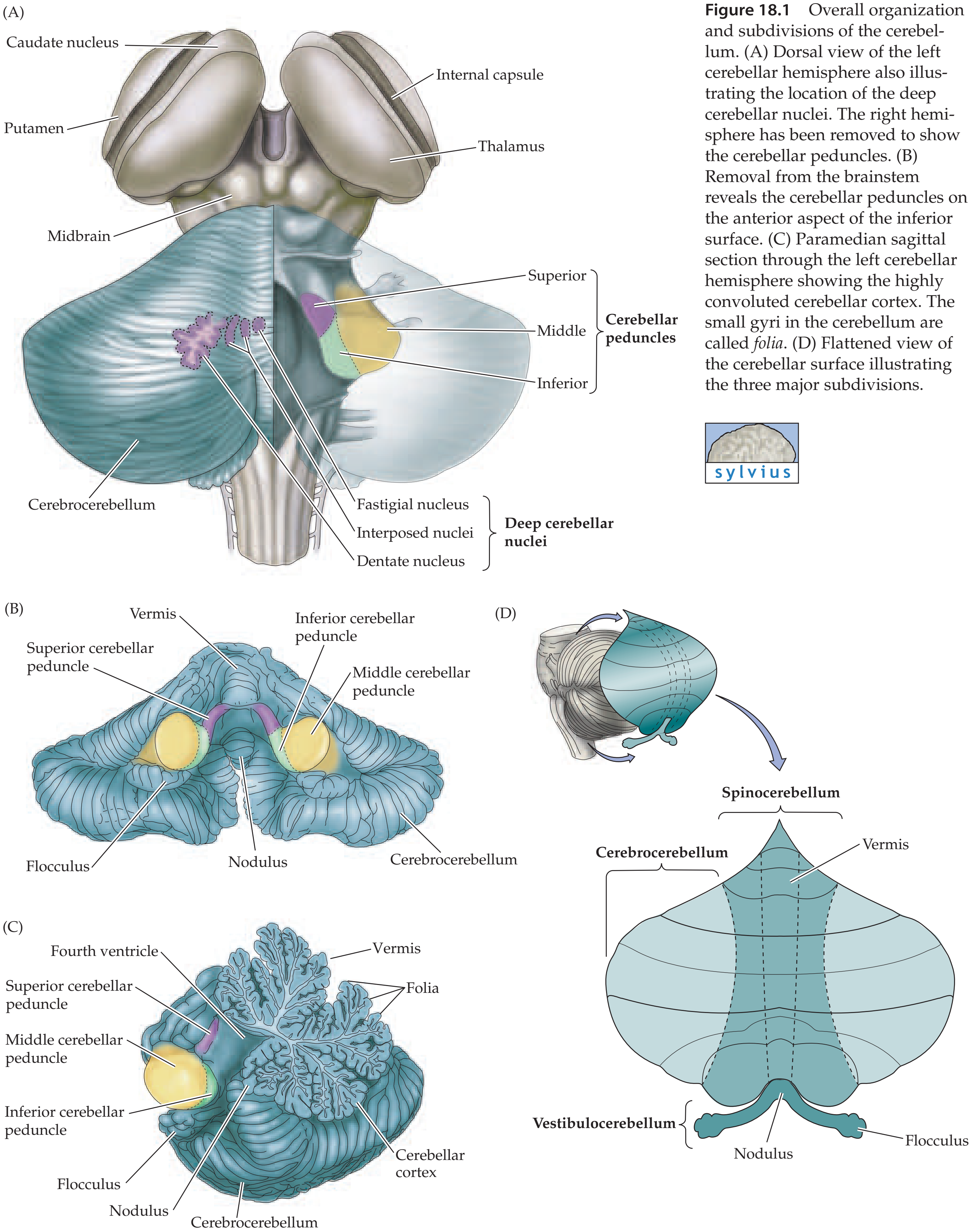

(A)
Caudate nucleus
Internal capsule
Putamen
Thalamus
Midbrain
Superior
Middle
Inferior
Cerebellar peduncles
Cerebrocerebellum
Fastigial nucleus
Interposed nuclei
Dentate nucleus
Deep cerebellar nuclei
(B)
Vermis
Superior cerebellar peduncle
Inferior cerebellar peduncle
Middle cerebellar peduncle
Flocculus
Nodulus
Cerebrocerebellum
(C)
Fourth ventricle
Vermis
Superior cerebellar peduncle
Folia
Middle cerebellar peduncle
Inferior cerebellar peduncle
Cerebellar cortex
Flocculus
Nodulus
Cerebrocerebellum
(D)
Spinocerebellum
Cerebrocerebellum
Vermis
Vestibulocerebellum
Nodulus
Flocculus

Figure 18.1 Overall organization and subdivisions of the cerebellum. (A) Dorsal view of the left cerebellar hemisphere also illustrating the location of the deep cerebellar nuclei. The right hemisphere has been removed to show the cerebellar peduncles. (B) Removal from the brainstem reveals the cerebellar peduncles on the anterior aspect of the inferior surface. (C) Paramedian sagittal section through the left cerebellar hemisphere showing the highly convoluted cerebellar cortex. The small gyri in the cerebellum are called *folia*. (D) Flattened view of the cerebellar surface illustrating the three major subdivisions.

the regulation of movements underlying posture and equilibrium. The last of the major subdivisions is the **spinocerebellum**. The spinocerebellum occupies the median and paramedian zone of the cerebellar hemispheres and is the only part that receives input directly from the spinal cord. The lateral part of the spinocerebellum is primarily concerned with movements of distal muscles, such as the relatively gross movements of the limbs in walking. The central part, called the **vermis**, is primarily concerned with movements of proximal muscles, and also regulates eye movements in response to vestibular inputs.

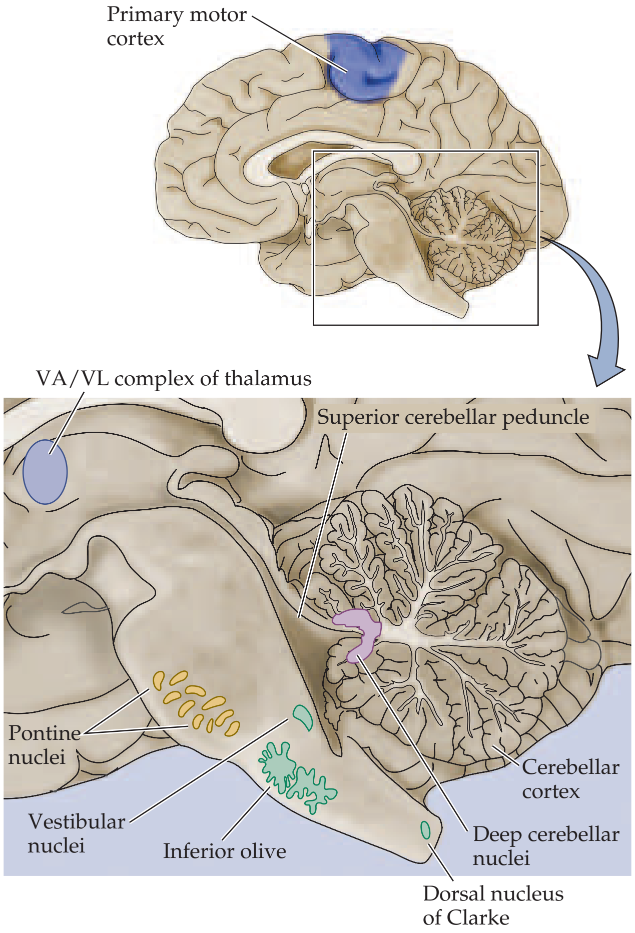
The connections between the cerebellum and other parts of the nervous system occur by way of three large pathways called **cerebellar peduncles** (Figures 18.1 to 18.3). The **superior cerebellar peduncle** (or **brachium conjunctivum**) is almost entirely an efferent pathway. The neurons that give rise to this pathway are in the deep cerebellar nuclei, and their axons project to upper motor neurons in the red nucleus, the deep layers of the superior colliculus, and, after a relay in the dorsal thalamus, the primary motor and premotor areas of the cortex (see Chapter 16). The **middle cerebellar peduncle** (or **brachium pontis**) is an afferent pathway to the cerebellum; most of the cell bodies that give rise to this pathway are in the base of the pons, where they form the **pontine nuclei** (Figure 18.2). The pontine nuclei receive input from a wide variety of sources, including almost all areas of the cerebral cortex and the superior colliculus. The axons of the pontine nuclei, called **transverse pontine fibers**, cross the midline and enter the cerebellum via the

TABLE 18.1
Major Components of the Cerebellum

Cerebellar cortex
- Cerebrocerebellum
- Spinocerebellum
- Vestibulocerebellum

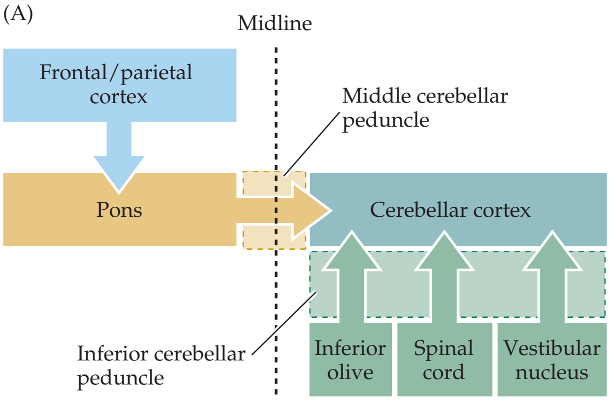
Deep cerebellar nuclei
- Dentate nucleus
- Interposed nuclei
- Fastigial nucleus

Cerebellar peduncles
- Superior peduncle
- Middle peduncle
- Inferior peduncle



sylvius

Figure 18.2 Components of the brainstem and diencephalon related to the cerebellum. This sagittal section shows the major structures of the cerebellar system, including the cerebellar cortex, the deep cerebellar nuclei, and the ventroanterior and ventrolateral (VA/VL) complex (which is the target of some of the deep cerebellar nuclei).


(A)
Midline
Frontal/parietal cortex
Middle cerebellar peduncle
Pons
Cerebellar cortex
Inferior cerebellar peduncle
Inferior olive
Spinal cord
Vestibular nucleus

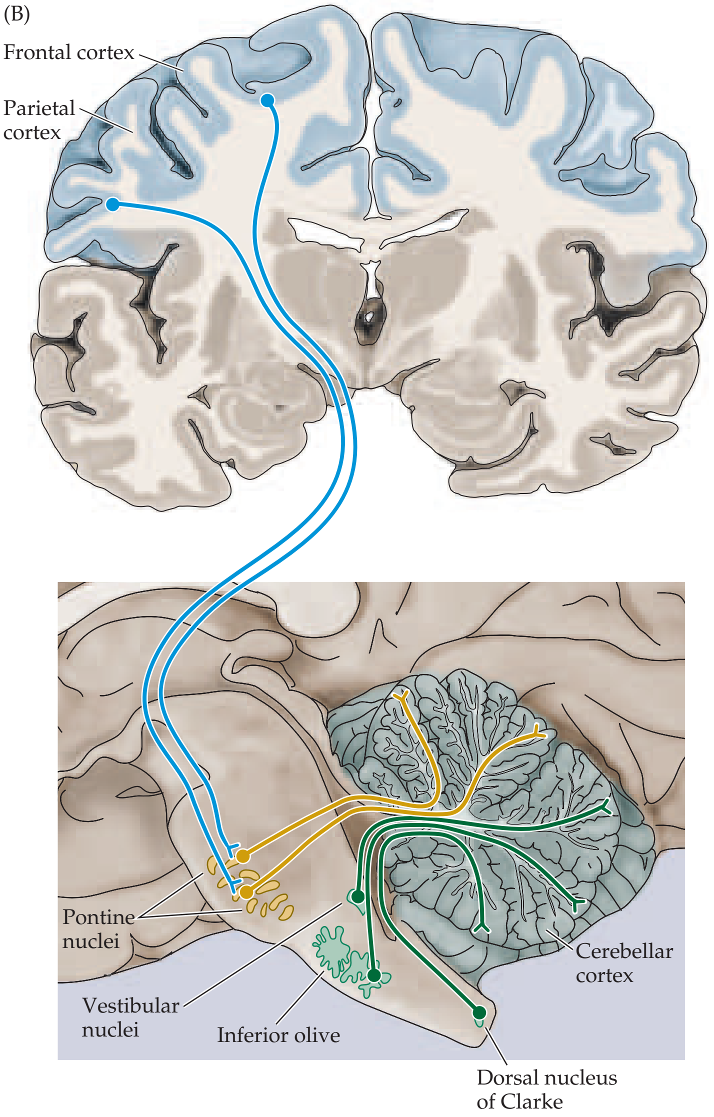

(B)
Frontal cortex
Parietal cortex
Pontine nuclei
Cerebellar cortex
Vestibular nuclei
Inferior olive
Dorsal nucleus of Clarke

Figure 18.3 Functional organization of the inputs to the cerebellum. (A) Diagram of the major inputs. (B) Idealized coronal and sagittal sections through the human brainstem and cerebrum, showing inputs to the cerebellum from the cortex, vestibular system, spinal cord, and brainstem. The cortical projections to the cerebellum are made via relay neurons in the pons. These pontine axons then cross the midline within the pons and run to the cerebellum via the middle cerebellar peduncle. Axons from the inferior olive, spinal cord, and vestibular nuclei enter via the inferior cerebellar peduncle.

TABLE 18.2

Major inputs to the Cerebellum (via Inferior and Middle Cerebellar Peduncles)

From cerebral cortex:

- Parietal cortex (secondary visual, primary and secondary somatic sensory)
- Cingulate cortex (limbic)
- Frontal cortex (primary and secondary motor)

Other sources:

- Red nucleus
- Superior colliculus
- Spinal cord (Clarke's column)
- Vestibular labyrinth and nuclei
- Reticular formation
- Inferior olivary nucleus
- Locus ceruleus

middle cerebellar peduncle (Figure 18.3). Each of the two middle cerebellar peduncles contain over 20 million axons, making this one of the largest pathways in the brain. In comparison, the optic and pyramidal tracts contain only about a million axons. Most of these pontine axons relay information from the cortex to the cerebellum. Finally, the **inferior cerebellar peduncle** (or **restiform body**) is the smallest but most complex of the cerebellar peduncles, containing multiple afferent and efferent pathways. Efferent pathways in this peduncle project to the vestibular nuclei and the reticular formation; the afferent pathways include axons from the vestibular nuclei, the spinal cord, and several regions of the brainstem tegmentum.

Projections to the Cerebellum

The cerebral cortex is by far the largest source of inputs to the cerebellum, and the major destination of these inputs is the cerebrocerebellum (see Figure 18.3 and Table 18.2). These pathways arise from a somewhat more circumscribed area of the cortex than do those to the basal ganglia (see Chapter 17). The majority originate in the primary motor and premotor cortices of

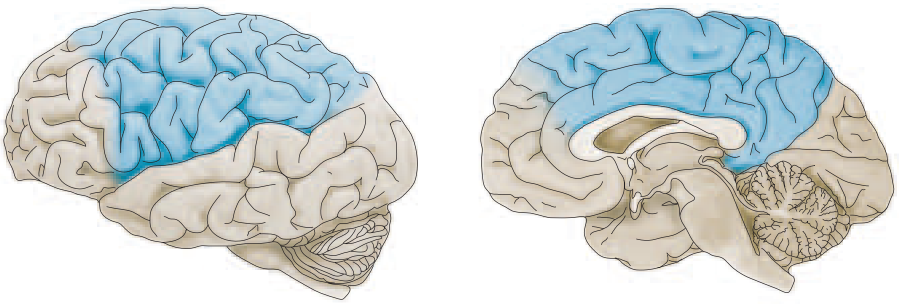


Figure 18.4 Regions of the cerebral cortex that project to the cerebellum (shown in blue). The cortical projections to the cerebellum are mainly from the sensory association cortex of the parietal lobe and motor association areas of the frontal lobe.

the frontal lobe, the primary and secondary somatic sensory cortices of the anterior parietal lobe, and the secondary visual regions of the posterior parietal lobe (Figure 18.4). The visual input to the cerebellum originates mostly in association areas concerned with processing moving visual stimuli (i.e., the cortical targets of the magnocellular stream; see Chapter 11). Indeed, visually guided coordination of ongoing movement is one of the major tasks carried out by the cerebrocerebellum. Most of these cortical pathways relay in the pontine nuclei before entering the cerebellum (see Figure 18.3).

Sensory pathways also project to the cerebellum (see Figure 18.3 and Table 18.2). Vestibular axons from the eighth cranial nerve and axons from the vestibular nuclei in the medulla project to the vestibulocerebellum. In addition, relay neurons in the **dorsal nucleus of Clarke** in the spinal cord (a group of relay neurons innervated by proprioceptive axons from the periphery; see Chapter 8) send their axons to the spinocerebellum. The vestibular and spinal inputs provide the cerebellum with information from the labyrinth in the ear, from muscle spindles, and from other mechanoreceptors that monitor the position and motion of the body. The somatic sensory input remains topographically mapped in the spinocerebellum such that there are orderly representations of the body surface within the cerebellum (Figure 18.5). These maps are "fractured," however: That is, fine-grain electrophysiological analysis indicates that each small area of the body surface is represented multiple times by spatially separated clusters of cells rather than by a specific site within a single continuous topographic map of the body surface. The vestibular and spinal inputs remain ipsilateral from their point of entry

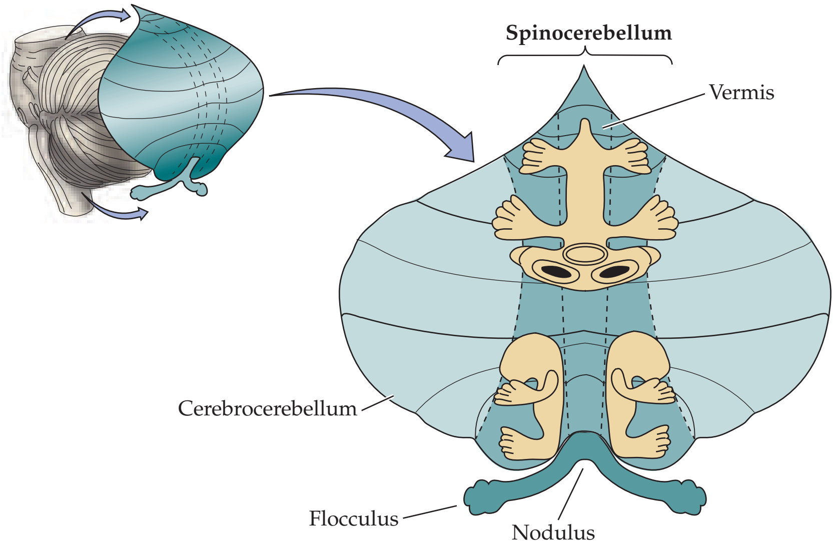


Figure 18.5 Somatotopic maps of the body surface in the cerebellum. The spinocerebellum contains at least two maps of the body.

in the brainstem, traveling in the inferior cerebellar peduncle (see Figure 18.3B). This arrangement ensures that, in contrast to most areas of the brain, the right cerebellum is concerned with the right half of the body and the left cerebellum with the left half.

Finally, the entire cerebellum receives modulatory inputs from the **inferior olive** and the locus ceruleus in the brainstem. These nuclei evidently participate in the learning and memory functions served by cerebellar circuitry.

Projections from the Cerebellum

Except for a direct projection from the vestibulocerebellum to the vestibular nuclei, the cerebellar cortex projects to the deep cerebellar nuclei, which project in turn to upper motor neurons in the cortex (via a relay in the thalamus) and in the brainstem (Figure 18.6 and Table 18.3). There are four major deep

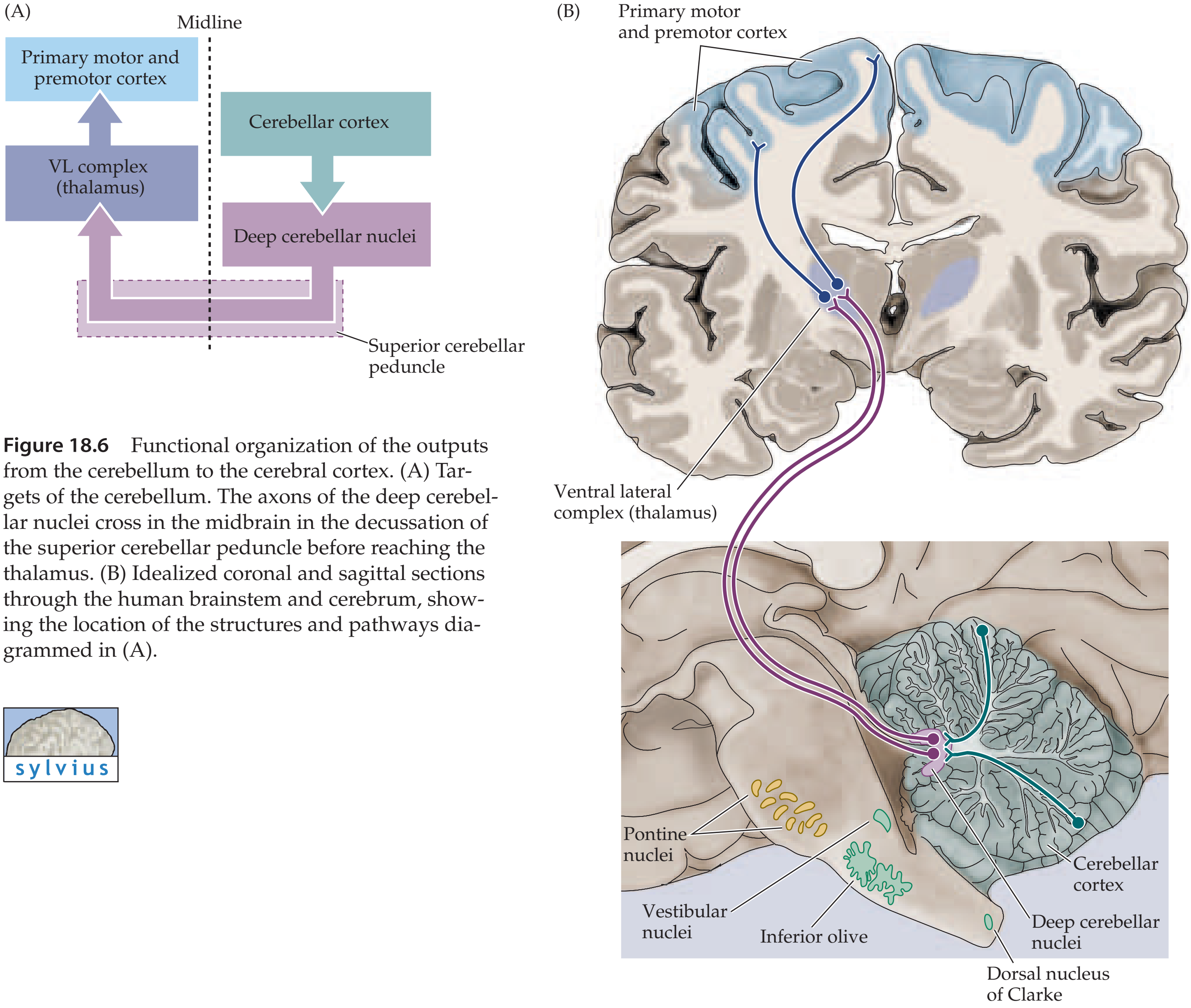

(A)
Midline
Primary motor and premotor cortex
Cerebellar cortex
VL complex (thalamus)
Deep cerebellar nuclei
Superior cerebellar peduncle
(B)
Primary motor and premotor cortex
Ventral lateral complex (thalamus)
Pontine nuclei
Vestibular nuclei
Inferior olive
Cerebellar cortex
Deep cerebellar nuclei
Dorsal nucleus of Clarke

Figure 18.6 Functional organization of the outputs from the cerebellum to the cerebral cortex. (A) Targets of the cerebellum. The axons of the deep cerebellar nuclei cross in the midbrain in the decussation of the superior cerebellar peduncle before reaching the thalamus. (B) Idealized coronal and sagittal sections through the human brainstem and cerebrum, showing the location of the structures and pathways diagrammed in (A).

nuclei: the **dentate nucleus** (by far the largest), two **interposed nuclei,** and the **fastigial nucleus**. Each receives input from a different region of the cerebellar cortex. Although the borders are not distinct, in general, the cerebrocerebellum projects primarily to the dentate nucleus, the spinocerebellum to the interposed nuclei, and the vestibulocerebellum to the fastigial nucleus. Pathways from the dentate nucleus are destined for the cortex via a relay in the ventral nuclear complex in the thalamus. Since each cerebellar hemisphere is concerned with the ispsilateral side of the body, this pathway must cross the midline if the motor cortex in each hemisphere, which is concerned with contralateral musculature, is to receive information from the appropriate cerebellum. Consequently, the dentate axons exit the cerebellum via the superior cerebellar peduncle, cross at the **decussation of the superior cerebellar peduncle** in the caudal midbrain, and then ascend to the thalamus.

TABLE 18.3
Output Targets of the Cerebellum

Red nucleus
Vestibular nuclei
Superior colliculus
Reticular formation
Motor cortex (via relay in ventral lateral nuclei of thalamus)

The thalamic nuclei that receive projections from the deep cerebellar nuclei are segregated in two distinct subdivisions of the ventral lateral nuclear complex: the oral, or anterior, part of the posterolateral segment, and a region simply called "area X." Both of these thalamic relays project directly to primary motor and premotor association cortices. Thus, the cerebellum has access to the upper motor neurons that organize the sequence of muscular contractions underlying complex voluntary movements (see Chapter 16). Pathways leaving the deep cerebellar nuclei also project to upper motor neurons in the red nucleus, the superior colliculus, the vestibular nuclei, and the reticular formation (see Table 18.3 and Chapter 16).

Anatomical studies using viruses to trace chains of connections between nerve cells have shown that large parts of the cerebrocerebellum send information back to non-motor areas of the cortex to form "closed loops." That is, a region of the cerebellum projects back to the same cortical area that in turn projects to it. These closed loops run in parallel to "open loops" that receive input from multiple cortical areas and funnel output back to upper motor neurons in specific regions of the motor and premotor cortices (Figure 18.7).

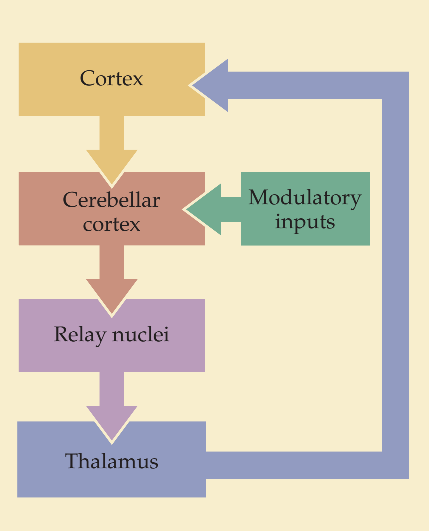
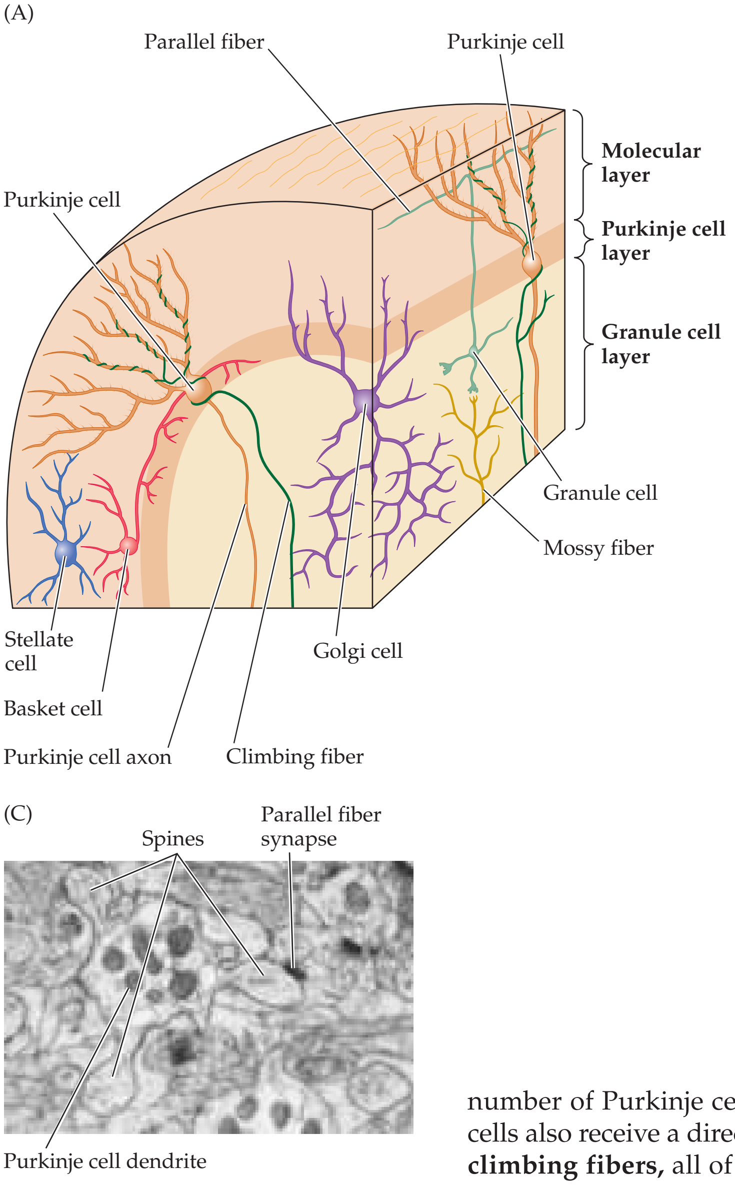


Figure 18.7 Summary diagram of motor modulation by the cerebrocerebellum. The central processing component, the cerebrocerebellar cortex, receives massive input from the cerebral cortex and generates signals that adjust the responses of upper motor neurons to regulate the course of a movement. Note that modulatory inputs also influence the processing of information within the cerebellar cortex. The output signals from the cerebellar cortex are relayed indirectly to the thalamus and then back to the motor cortex, where they modulate the motor commands.

Circuits within the Cerebellum

The ultimate destination of the afferent pathways to the cerebellar cortex is a distinctive cell type called the **Purkinje cell** (Figure 18.8). However, the input from the cerebral cortex to the Purkinje cells is indirect. Neurons in the pontine nuclei receive a projection from the cerebral cortex and then relay the information to the contralateral cerebellar cortex. The axons from the pontine nuclei and other sources are called **mossy fibers** because of the appearance of their synaptic terminals**.** Mossy fibers synapse on **granule cells** in the granule cell layer of the cerebellar cortex (see Figures 18.8 and 18.9). The cerebellar granule cells are widely held to be the most abundant class of neurons in the human brain. They give rise to specialized axons called **parallel fibers** that ascend to the **molecular layer** of the cerebellar cortex. The parallel fibers bifurcate in the molecular layer to form T-shaped branches that relay information via excitatory synapses onto the dendritic spines of the Purkinje cells.

The Purkinje cells present the most striking histological feature of the cerebellum. Elaborate dendrites extend into the molecular layer from a single subjacent layer of these giant nerve cell bodies (called the Purkinje layer). Once in the molecular layer, the Purkinje cell dendrites branch extensively in a plane at right angles to the trajectory of the parallel fibers (Figure 18.8A). In this way, each Purkinje cell is in a position to receive input from a large number of parallel fibers, and each parallel fiber can contact a very large


(A)
Parallel fiber
Purkinje cell
Purkinje cell
Molecular layer
Purkinje cell layer
Granule cell layer
Granule cell
Mossy fiber
Stellate cell
Golgi cell
Basket cell
Purkinje cell axon
Climbing fiber
(C)
Spines
Parallel fiber synapse
Purkinje cell dendrite

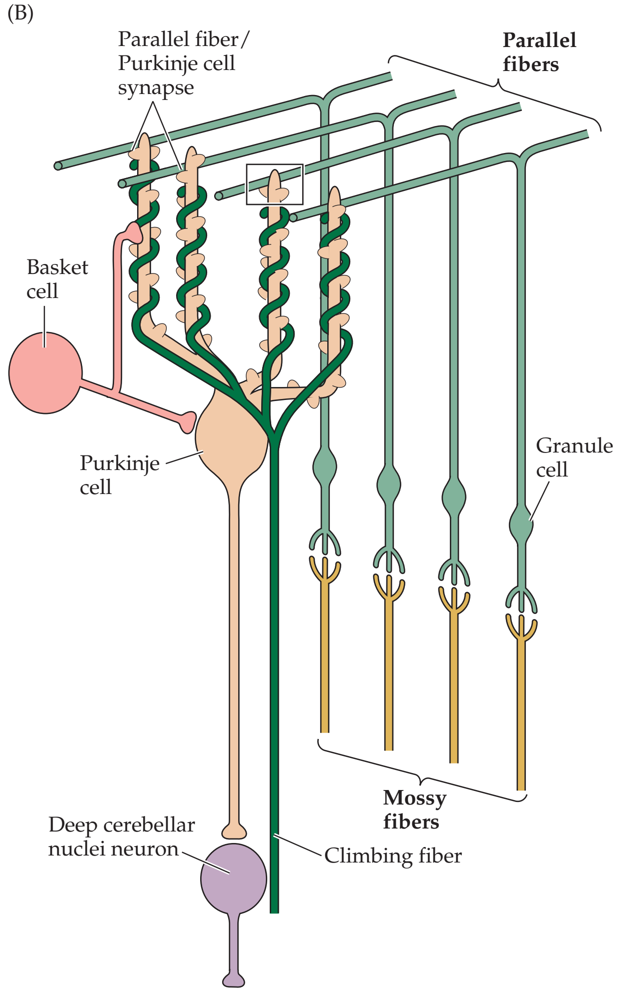

(B)
Parallel fiber/ Purkinje cell synapse
Parallel fibers
Basket cell
Purkinje cell
Granule cell
Mossy fibers
Deep cerebellar nuclei neuron
Climbing fiber

Figure 18.8 Neurons and circuits of the cerebellum. (A) Neuronal types in the cerebellar cortex. Note that the various neuron classes are found in distinct layers. (B) Diagram showing convergent inputs onto the Purkinje cell from parallel fibers and local circuit neurons [boxed region shown at higher magnification in (C)]. The output of the Purkinje cells is to the deep cerebellar nuclei. (C) Electron micrograph showing Purkinje cell dendritic shaft with three spines contacted by synapses from a trio of parallel fibers. (C courtesy of A. S. La Mantia and P. Rakic.)

number of Purkinje cells (on the order of tens of thousands). The Purkinje cells also receive a direct modulatory input on their dendritic shafts from the **climbing fibers,** all of which arise in the inferior olive (Figure 18.8B). Each Purkinje cell receives numerous synaptic contacts from a single climbing fiber. In most models of cerebellum function, the climbing fibers regulate movement by modulating the effectiveness of the mossy-parallel fiber connection with the Purkinje cells.

The Purkinje cells project in turn to the deep cerebellar nuclei. They are the only output cells of the cerebellar cortex. Since Purkinje cells are GABAergic, the output of the cerebellar cortex is wholly inhibitory. However, the neurons in the deep cerebellar nuclei receive excitatory input from the collaterals of the mossy and climbing fibers. The Purkinje cell inhibition of the deep nuclei neurons serves to modulate the level of this excitation (Figure 18.9).

Inputs from local circuit neurons modulate the inhibitory activity of Purkinje cells and occur on both dendritic shafts and the cell body. The most powerful of these local inputs are inhibitory complexes of synapses made around the Purkinje cell bodies by **basket cells** (see Figure 18.8A,B). Another type of local circuit neuron, the **stellate cell**, receives input from the parallel fibers and provides an inhibitory input to the Purkinje cell dendrites. Finally, the molecular layer contains the apical dendrites of a cell type called **Golgi cells**; these neurons have their cell bodies in the granular cell layer. The Golgi cells receive input from the parallel fibers and provide an inhibitory feedback to the cells of origin of the parallel fibers (the granule cells).

This basic circuit is repeated over and over throughout every subdivision of the cerebellum in all mammals and is the fundamental functional module of the cerebellum. Modulation of signal flow through these modules provides the basis for both real-time regulation of movement and the long-term changes in regulation that underlie motor learning. The flow of signals through this admittedly complex intrinsic circuitry is best described in reference to the Purkinje cells (see Figure 18.9). The Purkinje cells receive two types of excitatory input from outside of the cerebellum, one directly from the climbing fibers and the other indirectly via the parallel fibers of the granule cells. The Golgi, stellate, and basket cells control the flow of information through the cerebellar cortex. For example, the Golgi cells form an inhibitory feedback that may limit the duration of the granule cell input to the Purkinje cells, whereas the basket cells provide lateral inhibition that may focus the

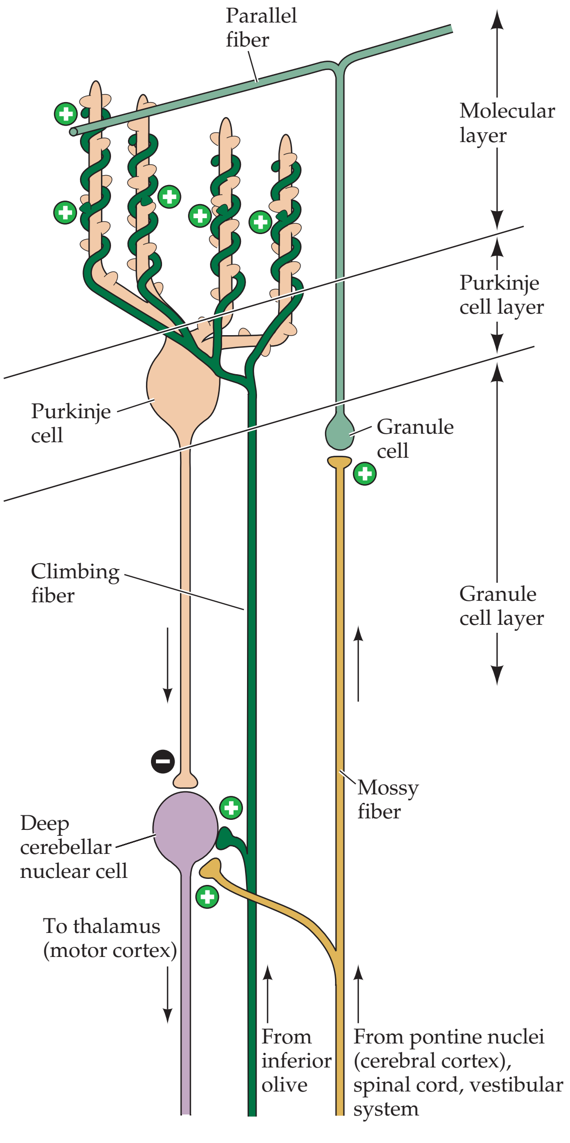

Parallel fiber
Molecular layer
Purkinje cell layer
Purkinje cell
Granule cell
Granule cell layer
Climbing fiber
Mossy fiber
Deep cerebellar nuclear cell
To thalamus (motor cortex)
From inferior olive
From pontine nuclei (cerebral cortex), spinal cord, vestibular system

Figure 18.9 Excitatory and inhibitory connections in the cerebellar cortex and deep cerebellar nuclei. The excitatory input from mossy fibers and climbing fibers to Purkinje cells and deep nuclear cells is basically the same. Additional convergent input onto the Purkinje cell from local circuit neurons (basket and stellate cells) and other Purkinje cells establishes a basis for the comparison of ongoing movement and sensory feedback derived from it. The Purkinje cell output to the deep cerebellar nuclear cell thus generates an error correction signal that can modify movements already begun. The climbing fibers modify the efficacy of the parallel fiber–Purkinje cell connection, producing long-term changes in cerebellar output. (After Stein, 1986.)

Box A
Prion Diseases

Creutzfeldt-Jakob disease (CJD) is a rare but devastating neurological disorder characterized by cerebellar ataxia, myoclonic jerks, seizures, and the fulminant progression of dementia. The onset is usually in middle age, and death typically follows within a year. The distinctive histopathology of the disease, termed "spongiform degeneration," consists of neuronal loss and extensive glial proliferation, mainly in the cortex of the cerebellum and cerebrum; the peculiar spongiform pattern is due to vacuoles in the cytoplasm of neurons and glia. CJD is the only human disease known to be transmitted by inoculation (either orally or into the bloodstream) *or* inherited through the germline! In contrast to other transmissible diseases mediated by microorganisms such as viruses or bacteria, the agent in this case is a protein called a prion.

Observations dating back some 30 years suggested that CJD was infective. The major clue came from scrapie, a once-obscure disease of sheep that is also characterized by cerebellar ataxia, wasting, and intense itching. The ability to transmit scrapie from one sheep to another strongly suggested an infectious agent. Another clue came from the work of Carlton Gajdusek, a neurologist studying a peculiar human disease called kuru that occurred specifically in a group of New Guinea natives known to practice ritual cannibalism. Like CJD, kuru is a neurodegenerative disease characterized by devastating cerebellar ataxia and subsequent dementia, usually leading to death within a year. The striking similarities in the distinctive histopathology of scrapie and kuru—namely spongiform degeneration—suggested a common pathogenesis and led to the successful transmission of kuru to apes and chimpanzees in the 1960s, confirming that CJD was indeed infectious. The prolonged period between inoculation and disease onset (months to years) led Gajdusek to suggest that the transmissible agent was what he called a "slow virus."

These extraordinary findings spurred an intensive search for the infectious agent. The transmission of scrapie from sheep to hamsters by Stanley Prusiner at the University of California at San Francisco permitted biochemical characterization of partially purified fractions of scrapie agent from hamster brain. Oddly, he found that the infectivity was extraordinarily resistant to ultraviolet irradiation or nucleases, both treatments that degrade nucleic acids. It therefore seemed unlikely that a virus could be the causal agent. Conversely, procedures that modified or degraded proteins markedly diminished infectivity. In 1982, Prusiner coined the term *prion* to refer to the agent causing these transmissible spongiform encephalopathies. He chose the term to emphasize that the agent was a proteinaceous infectious particle (he made the abbreviation a little more euphonious in the process). Subsequently, a half dozen more diseases of animals—including the widely publicized bovine spongiform encephalopathy (BSE), or "mad cow disease"—and four more human diseases have been shown to be caused by prions.

Whether prions contain undetected nucleic acids or are really proteins remained controversial for some years. Prusiner strongly advocated a "protein only" hypothesis, a revolutionary concept with respect to transmissible diseases. He proposed that the prion is a protein consisting of a modified (scrapie) form (PrP^{Sc}) of the normal host protein (PrP^{C}, for "prion protein control"), the propagation of which occurs by a conformational change of endogenous PrP^{C} to PrP^{Sc} autocatalyzed by PrP^{Sc}. That is, the modified form of the protein (PrP^{Sc}) transforms the normal form (PrP^{C}) into the modified form, much as crystals form in supersaturated solutions. Differences in the secondary structure of PrP^{C} and PrP^{Sc} evident by optical spectroscopy supported this idea. An alternative hypothesis, however, was that the agent is simply an unconventional nucleic acid-containing virus, and that the accumulation of PrP^{Sc} is an incidental consequence of infection and cell death.

A compelling body of evidence in support of the "protein only" hypothesis has emerged only in the past decade. First, PrP^{Sc} and scrapie infectivity copurify by a number of procedures, including affinity chromatography using an anti-PrP monoclonal antibody; no nucleic acid has been detected in highly purified preparations, despite intensive efforts. Second, spongiform encephalopathies can be inherited in humans, and the cause is now known to be a mutation (or mutations) in the gene coding for PrP. Third, transgenic mice carrying a mutant *PrP* gene equivalent to one of the mutations of inherited human prion disease develop a spongiform encephalopathy. Thus, a defective protein is sufficient to account for the disease. Finally, transgenic mice carrying a null mutation for *PrP* do not develop spongiform encephalopathy when inoculated with scrapie agent, whereas wild-type mice do. These results argue convincingly that PrP^{Sc} must indeed interact with endogenous PrP^{C} to convert PrP^{C} to PrP^{Sc}, propagating the disease in the process. The protein is highly conserved across mammalian species, suggesting that it serves some essential function, although mice carrying a null mutation of *PrP* exhibit no detectable abnormalities.

These advances notwithstanding, many questions remain. What is the mechanism by which the conformational transformation of PrP^{C} to PrP^{Sc} occurs? How do mutations at different sites of the same protein culminate in the distinct phenotypes evident in diverse prion diseases of humans? Are conformational changes of proteins a common mechanism of other neurodegenerative diseases? And do these findings suggest a therapy for the dreadful manifestations of spongiform encephalopathies?

Despite these unanswered questions, this work remains one of the most exciting chapters in modern neurological research, and rightly won Nobel Prizes in Physiology or Medicine for both Gajdusek (in 1976) and Prusiner (in 1997).

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spatial distribution of Purkinje cell activity. The Purkinje cells modulate the activity of the deep cerebellar nuclei, which are driven by the direct excitatory input they receive from the collaterals of the mossy and climbing fibers.

The modulation of cerebellar output also occurs at the level of the Purkinje cells (see Figure 18.9). This latter modulation may be responsible for the motor learning aspect of cerebellar function. According to a model proposed by Masao Ito and his colleagues at Tokyo University, the climbing fibers relay the message of a motor error to the Purkinje cells. This message produces long-term reductions in the Purkinje cell responses to mossy-parallel fiber inputs. This inhibitory effect on the Purkinje cell responses *disinhibits* the deep cerebellar nuclei (for an account of the probable cellular mechanism for this long-term reduction in the efficacy of the parallel fiber synapse on Purkinje cells; see Chapter 24). As a result, the output of the cerebellum to the various sources of upper motor neurons is enhanced, in much the way that this process occurs in the basal ganglia (see Chapter 17).

Cerebellar Circuitry and the Coordination of Ongoing Movement

As expected for a structure that monitors and regulates motor behavior, neuronal activity in the cerebellum changes continually during the course of a movement. For instance, the execution of a relatively simple task like flipping the wrist back and forth elicits a dynamic pattern of activity in both the Purkinje cells and the deep cerebellar nuclear cells that closely follows the ongoing movement (Figure 18.10). Both types of cells are tonically active at rest and change their frequency of firing as movements occur. The neurons respond selectively to various aspects of movement, including extension or contraction of specific muscles, the position of the joints, and the direction of the next movement that will occur. All this information is therefore encoded by changes in the firing frequency of Purkinje cells and deep cerebellar nuclear cells.

As these neuronal response properties predict, cerebellar lesions and disease tend to disrupt the modulation and coordination of ongoing movements (Box A). Thus, the hallmark of patients with cerebellar damage is difficulty producing smooth, well-coordinated movements. Instead, movements tend to be jerky and imprecise, a condition referred to as **cerebellar ataxia**. Many of these difficulties in performing movements can be explained as disruption of the cerebellum's role in correcting errors in ongoing movements. Normally, the cerebellar error correction mechanism ensures that move-

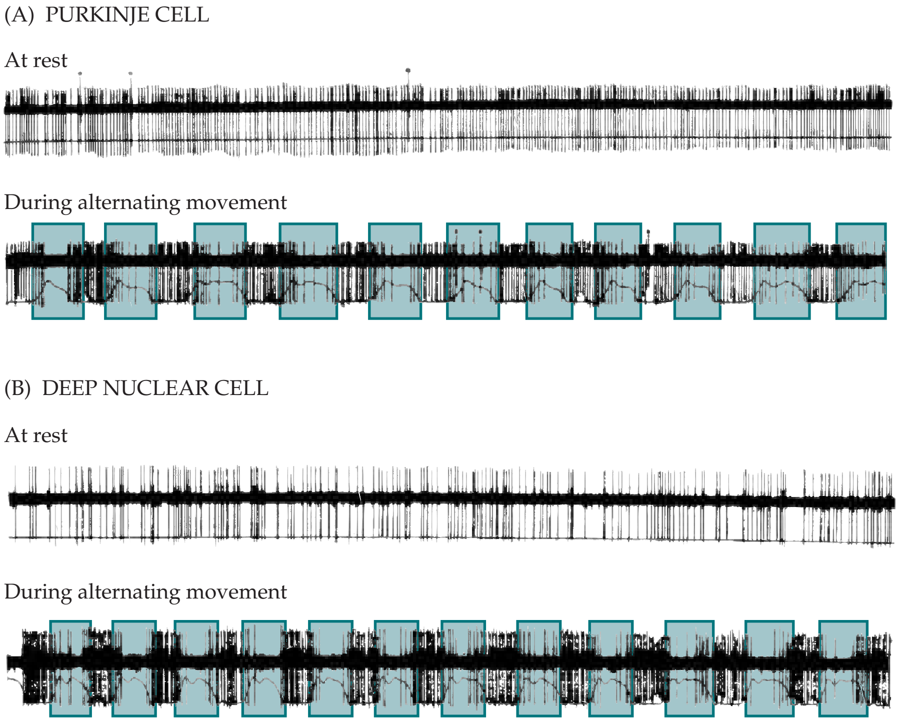


Figure 18.10 Activity of Purkinje cells (A) and deep cerebellar nuclear cells (B) at rest (upper traces) and during movement of the wrist (lower traces). The lines below the action potential records show changes in muscle tension, recorded by electromyography. The durations of the wrist movements are indicated by the colored blocks. Both classes of cells are tonically active at rest. Rapid alternating movements result in the transient inhibition of the tonic activity of both cell types. (After Thach, 1968.)

ments are modified to cope with changing circumstances. As described earlier, the Purkinje cells and the deep cerebellar nuclear cells recognize potential errors by comparing patterns of convergent activity that are concurrently available to both cell types; the deep nuclear cells then send corrective signals to the upper motor neurons in order to maintain or improve the accuracy of the movement.

As in the case of the basal ganglia, studies of the oculomotor system (saccades in particular) have contributed greatly to understanding the contribution that the cerebellum makes to motor error reduction. For example, cutting part of the tendon to the lateral rectus muscles in one eye of a monkey weakens horizontal eye movements by that eye (Figure 18.11). When a patch is then placed over the normal eye to force the animal to use its weak eye, the saccades performed by the weak eye are initially *hypometric*; as expected, they fall short of visual targets. Then, over the next few days, the amplitude of the saccades gradually increases until they again become accurate. If the patch is then switched to cover the weakened eye, the saccades performed by the normal eye are now *hypermetric***.** In other words, over a period of a few days the nervous system corrects the error in the saccades made by the weak eye by increasing the gain in the saccade motor system. Lesions in the vermis of the spinocerebellum (see Figure 18.1) eliminate this ability to reduce the motor error.

Similar evidence of the cerebellar contribution to movement has come from studies of the vestibulo-ocular reflex (VOR) in monkeys and humans. The VOR works to keep the eyes trained on a visual target during head movements (see Chapter 13). The relative simplicity of this reflex has made it possible to analyze some of the mechanisms that enable motor learning as a process of error reduction. When a visual image on the retina shifts its position as a result of head movement, the eyes must move at the same velocity in the opposite direction to maintain a stable percept. In these studies, the

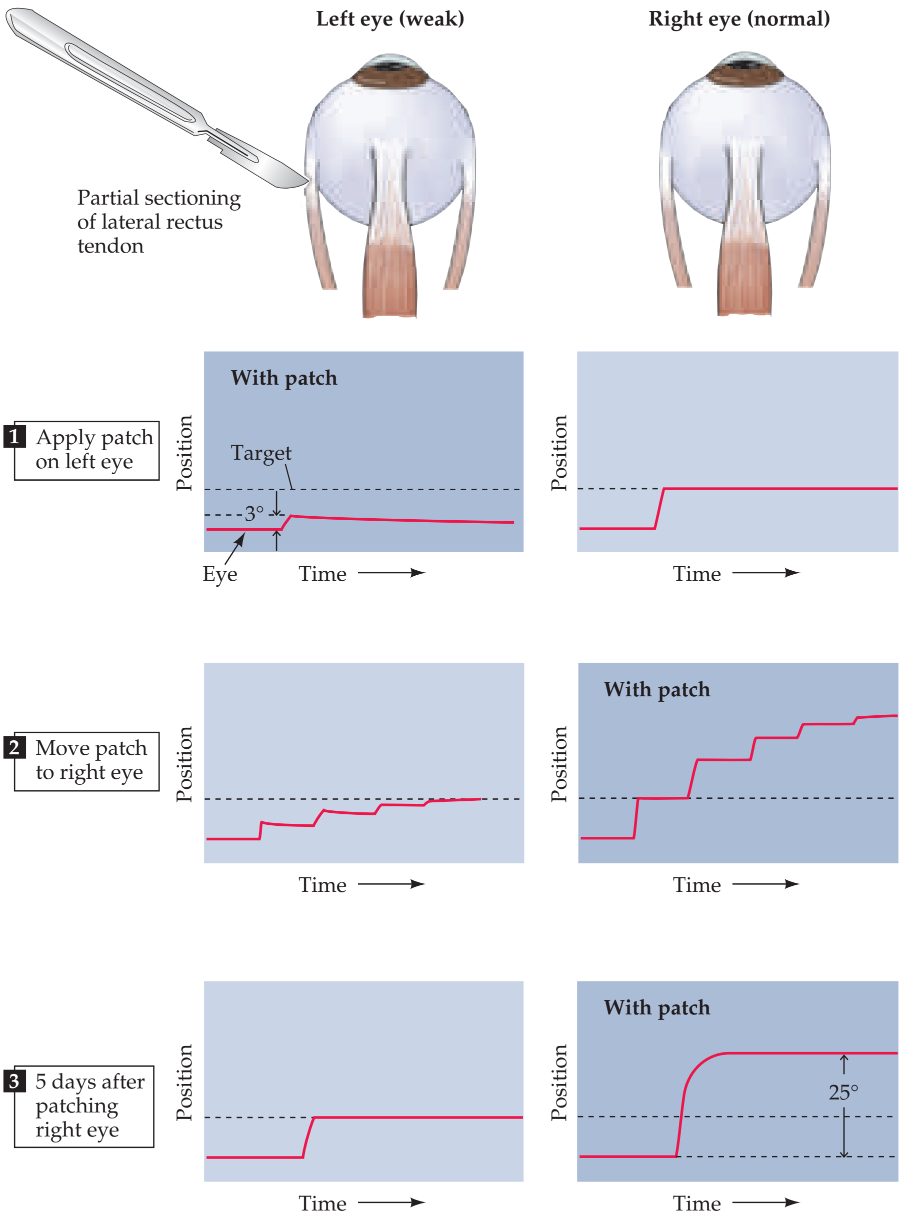
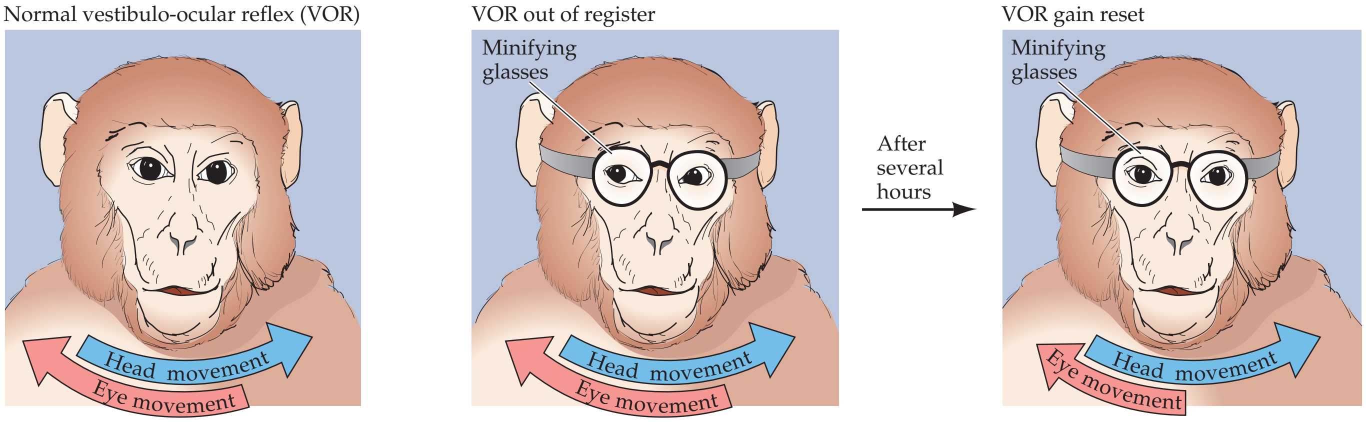

Left eye (weak)
Right eye (normal)
Partial sectioning of lateral rectus tendon
1 Apply patch on left eye
With patch
Target
3°
Eye
Position
Time
2 Move patch to right eye
With patch
Position
Time
3 5 days after patching right eye
With patch
25°
Position
Time

Figure 18.11 Contribution of the cerebellum to the experience-dependent modification of saccadic eye movements. Weakening of the lateral rectus muscle of the left eye causes the eye to undershoot the target (1). When the experimental subject (in this case a monkey) is forced to use this eye by patching the right eye, multiple saccades must be generated to acquire the target (2). After 5 days of experience with the weak eye, the gain of the saccadic system has been increased and a single saccade is now used to fixate the target. (3) This adjustment of the gain of the saccadic eye movement system depends on an intact cerebellum. (After Optican and Robinson, 1980.)

adaptability of the VOR to changes in the nature of incoming sensory information is challenged by fitting subjects (either monkeys or humans) with magnifying or minifying spectacles (Figure 18.12). Because the glasses alter the size of the visual image on the retina, the compensatory eye movements, which would normally have maintained a stable image of an object on the retina, are either too large or too small. Over time, subjects (whether monkeys or humans) learn to adjust the distance the eyes must move in response to head movements to accord with the artificially altered size of the visual field. Moreover, this change is retained for significant periods after the spectacles are removed and can be detected electrophysiologically in recordings from cerebellar Purkinje cells and neurons in the deep cerebellar nuclei. Information that reflects this change in the sensory context of the VOR must therefore be learned and remembered to eliminate the artificially introduced



Normal vestibulo-ocular reflex (VOR)

Head and eyes move in a coordinated manner to keep image on retina

VOR out of register

Eyes move too far in relation to image movement on the retina when the head moves

VOR gain reset

Eyes move smaller distances in relation to head movement to compensate

Figure 18.12 Learned changes in the vestibulo-ocular reflex in monkeys. Normally, this reflex operates to move the eyes as the head moves, so that the retinal image remains stable. When the animal observes the world through minifying spectacles, the eyes initially move too far with respect to the "slippage" of the visual image on the retina. After some practice, however, the VOR is reset and the eyes move an appropriate distance in relation to head movement, thus compensating for the altered size of the visual image.

error. Once again, if the cerebellum is damaged or removed, the ability of the VOR to adapt to the new conditions is lost. These observations support the conclusion that the cerebellum is critically important in error reduction during motor learning.

Cerebellar circuitry also provides real-time error correction during ongoing movements. This function is accomplished by changes in the tonically inhibitory activity of Purkinje cells that in turn influence the tonically excitatory deep cerebellar nuclear cells. The resulting effects on the ongoing activity of the deep cerebellar nuclear cells adjust the cerebellar output signals to the upper motor neurons in the cortex and brainstem.

Further Consequences of Cerebellar Lesions

As mentioned in the preceding discussion, patients with cerebellar damage, regardless of the causes or location, exhibit persistent errors in movement. These movement errors are always on the same side of the body as the damage to the cerebellum, reflecting the cerebellum's unusual status as a brain structure in which sensory and motor information is represented ipsilaterally rather than contralaterally. Furthermore, somatic, visual, and other inputs are represented topographically within the cerebellum; as a result, the movement deficits may be quite specific. For example, one of the most common cerebellar syndromes is caused by degeneration in the anterior portion of the cerebellar cortex in patients with a long history of alcohol abuse (Figure 18.13). Such damage specifically affects movement in the lower limbs, which are represented in the anterior spinocerebellum (see Figure 18.5). The consequences include a wide and staggering gait, with little impairment of arm or hand movements. Thus, the topographical organization of the cerebellum allows cerebellar damage to disrupt the coordination of movements performed by some muscle groups but not others.

The implication of these pathologies is that the cerebellum is normally capable of integrating the moment-to-moment actions of muscles and joints throughout the body to ensure the smooth execution of a full range of motor behaviors. Thus, cerebellar lesions lead first and foremost to a lack of coordination of ongoing movements (Box B). For example, damage to the vestibulocerebellum impairs the ability to stand upright and maintain the direction of gaze. The eyes have difficulty maintaining fixation; they drift from the target and then jump back with a corrective saccade, a phenomenon called **nystagmus**. Disruption of the pathways to the vestibular nuclei may also result in a loss of muscle tone. In contrast, patients with damage to the spinocerebellum have difficulty controlling walking movements; they have a wide-based gait with small shuffling movements, which represents the inappropriate operation of groups of muscles that normally rely on sensory feedback to produce smooth, concerted actions. The patients also have difficulty performing rapid alternating movements such as the heel-to-shin and/or finger-to-nose tests, a sign referred to as **dysdiadochokinesia**. Over- and underreaching may also occur (called **dysmetria**). During the movement, tremors—called **action** or **intention tremors**—accompany over- and undershooting of the movement due to disruption of the mechanism for detecting and correcting movement errors. Finally, lesions of the cerebrocerebellum produce impairments in highly skilled sequences of learned movements, such as speech or playing a musical instrument. The common denominator of all of these signs, regardless of the site of the lesion, is the inability to perform smooth, directed movements.

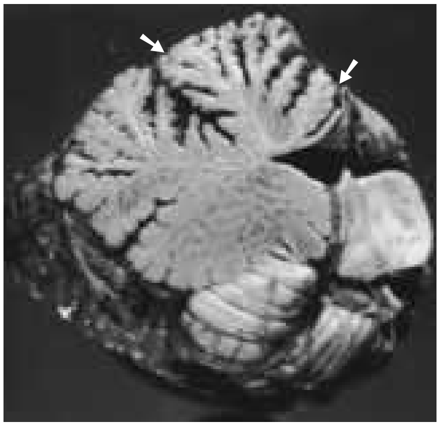


Figure 18.13 The pathological changes in a variety of neurological diseases provide insights about the function of the cerebellum. In this example, chronic alcohol abuse has caused degeneration of the anterior cerebellum (arrows), while leaving other cerebellar regions intact. The patient had difficulty walking but little impairment of arm movements or speech. The orientation of this paramedian sagittal section is the same as Figure 18.1C. (From Victor et al., 1959.)

Summary

The cerebellum receives input from regions of the cerebral cortex that plan and initiate complex and highly skilled movements; it also receives innervation from sensory systems that monitor the course of movements. This arrangement enables a comparison of an intended movement with the actual movement and a reduction in the difference, or "motor error." The corrections of motor error produced by the cerebellum occur both in real time and over longer periods, as motor learning. For example, the vestibulo-ocular reflex allows an observer to fixate an object of interest while the head moves; however, lenses that change image size produce a long-term change in the gain of this reflex that depends on an intact cerebellum. Knowledge of cerebellar circuitry suggests that motor learning is mediated by climbing fibers that ascend from the inferior olive to contact the dendrites of the Purkinje cells in the cerebellar cortex. Information provided by the climbing fibers modulates the effectiveness of the second major input to the Purkinje cells, which arrives via the parallel fibers from the granule cells. The granule cells receive information about the intended movement from the vast number of mossy fibers that enter the cerebellum from multiple sources, including the cortico-ponto-cerebellar pathway. As might be expected, the output of the cerebellum from the deep cerebellar nuclei projects to all the major sources of upper motor neurons described in Chapter 16. The effects of cerebellar disease provide strong support for the idea that the cerebellum regulates the performance of movements. Thus, patients with cerebellar disorders show severe ataxias in which the site of the lesion determines the particular movements affected.

Box B
Genetic Analysis of Cerebellar Function

Since the early 1950s, investigators interested in motor behavior have identified and studied strains of mutant mice in which movement is compromised. These mutant mice are easy to spot: following induced or spontaneous mutagenesis, the "screen" is simply to look for animals that have difficulty moving.

Genetic analysis suggested that some of these abnormal behaviors could be explained by single autosomal recessive or semidominant mutations, in which homozygotes are most severely affected. The strains were given names like *reeler, weaver, lurcher, staggerer*, and *leaner* that reflected the nature of the motor dysfunction they exhibited (see table). The relatively large number of mutations that compromise movement suggested it might be possible to understand some aspects of motor circuits and function at the genetic level.

A common feature of the mutants is ataxia resembling that associated with cerebellar dysfunction in humans. Indeed, all the mutations are associated with some form of cerebellar pathology. The pathologies associated with the *reeler* and *weaver* mutations are particularly striking. In the *reeler* cerebellum, Purkinje cells, granule cells, and interneurons are all displaced from their usual laminar positions, and there are fewer granule cells than normal. In *weaver*, most of the granule cells are lost prior to their migration from the external granule layer (a proliferative region where cerebellar granule cells are generated during development), leaving only Purkinje cells and interneurons to carry on the work of the cerebellum. Thus, these mutations causing deficits in motor behavior impair the development and final disposition of the neurons that comprise the major processing circuits of the cerebellum (see Figure 18.8).

Efforts to characterize the cellular mechanisms underlying these motor deficits were unsuccessful, and the molecular identity of the affected genes remained obscure until recently. In the past few years, however, both the *reeler* and *weaver* genes have been identified and cloned.

The *reeler* gene was cloned through a combination of good luck and careful observation. In the course of making transgenic mice by inserting DNA fragments in the mouse genome, investigators in Tom Curran's laboratory created a new strain of mice that behaved much like *reeler* mice and had similar cerebellar pathology. This "synthetic" *reeler* mutation was identified by finding the position of the novel DNA fragment—which turned out to be on the same chromo-

Motor Mutations in Mice

Mutation	*Inheritance*	*Chromosome affected*	*Behavioral and morphological characteristics*
reeler (*rl*)	Autosomal recessive	5	Reeling ataxia of gait, dystonic postures, and tremors. Systematic malposition of neuron classes in the forebrain and cerebellum. Small cerebellum, reduced number of granule cells.
weaver (*wv*)	Autosomal recessive	?	Ataxia, hypotonia, and tremor. Cerebellar cortex reduced in volume. Most cells of external granular layer degenerate prior to migration.
leaner (*tg*^{1a})	Autosomal recessive	8	Ataxia and hypotonia. Degeneration of granule cells, particularly in the anterior and nodular lobes of the cerebellum. Degeneration of a few Purkinje cells.
lurcher (*lr*)	Autosomal semidominant	6	Homozygote dies. Heterozygote is ataxic with hesitant, lurching gait and has seizures. Cerebellum half normal size; Purkinje cells degenerate; granule cells reduced in number.
nervous (*nr*)	Autosomal recessive	8	Hyperactivity and ataxia. Ninety percent of Purkinje cells die between 3 and 6 weeks of age.
Purkinje cell degeneration (*pcd*)	Autosomal recessive	13	Moderate ataxia. All Purkinje cells degenerate between the fifteenth embryonic day and third month of age.
staggerer (*sg*)	Autosomal recessive	9	Ataxia with tremors. Dendritic arbors of Purkinje cells are simple (few spines). No synapses of Purkinje cells with parallel fibers. Granule cells eventually degenerate.

(Adapted from Caviness and Rakic, 1978.)

some as the original *reeler* mutation. Further analysis showed that the same gene had indeed been mutated, and the *reeler* gene was subsequently identified. Remarkably, the protein encoded by this gene is homologous to known extracellular matrix proteins such as tenascin, laminin, and fibronectin (see Chapter 21). This finding makes good sense, since the pathophysiology of the *reeler* mutation entails altered cell migration, resulting in misplaced neurons in the cerebellar cortex as well as the cerebral cortex and hippocampus.

Molecular genetic techniques have also led to cloning the *weaver* gene. Using linkage analysis and the ability to clone and sequence large pieces of mammalian chromosomes, Andy Peterson and his colleagues "walked" (i.e., sequentially cloned) several kilobases of DNA in the chromosomal region to find where the *weaver* gene mapped. By comparing normal and mutant sequences within this region, they determined *weaver* to be a mutation in a K^+ channel that resembles the Ca^{2+}-activated K^+ channels found in cardiac muscle. How this particular molecule influences the development of granule cells or causes their death in the mutants is not yet clear.

The story of the proteins encoded by the *reeler* and *weaver* genes indicates both the promise and the challenge of a genetic approach to understanding cerebellar function. Identifying motor mutants and their pathology is reasonably straightforward, but understanding their molecular genetic basis depends on hard work and good luck.

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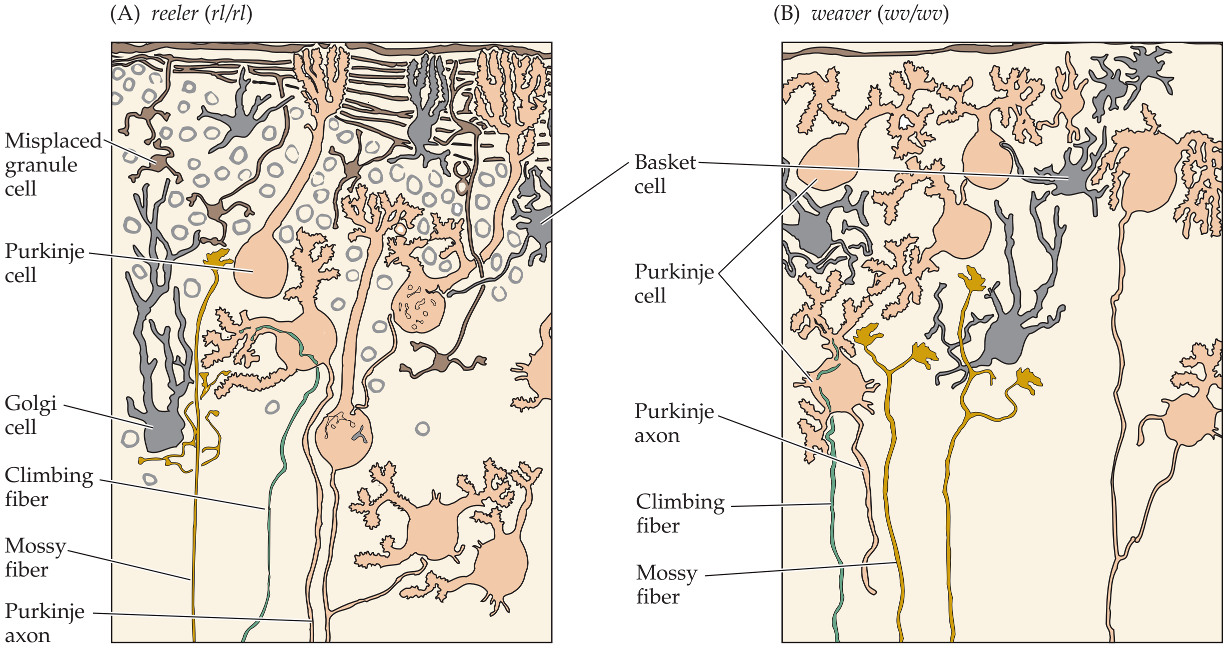
The cerebellar cortex is disrupted in both the *reeler* and *weaver* mutations. (A) The cerebellar cortex in homozygous *reeler* mice. The *reeler* mutation causes the major cell types of the cerebellar cortex to be displaced from their normal laminar positions. Despite the disorganization of the cerebellar cortex in *reeler* mutants, the major inputs—mossy fibers and climbing fibers—find appropriate targets. (B) The cerebellar cortex in homozygous *weaver* mice. The granule cells are missing, and the major cerebellar inputs synapse inappropriately on the remaining neurons. (After Rakic, 1977.)



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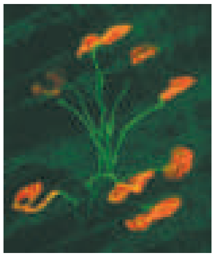
Chapter 19



Eye Movements and Sensory Motor Integration

Overview

Eye movements are, in many ways, easier to study than movements of other parts of the body. This fact arises from the relative simplicity of muscle actions on the eyeball. There are only six extraocular muscles, each of which has a specific role in adjusting eye position. Moreover, there are only four stereotyped kinds of eye movements, each with its own control circuitry. Eye movements have therefore been a useful model for understanding the mechanisms of motor control. Indeed, much of what is known about the regulation of movements by the cerebellum, basal ganglia, and vestibular system has come from the study of eye movements (see Chapters 13, 17, and 18). Here the major features of eye movement control are used to illustrate the principles of sensory motor integration that also apply to more complex motor behaviors.

What Eye Movements Accomplish

Eye movements are important in humans because high visual acuity is restricted to the fovea, the small circular region (about 1.5 mm in diameter) in the central retina that is densely packed with cone photoreceptors (see Chapter 10). Eye movements can direct the fovea to new objects of interest (a process called "foveation") or compensate for disturbances that cause the fovea to be displaced from a target already being attended to.

As demonstrated several decades ago by the Russian physiologist Alfred Yarbus, eye movements reveal a good deal about the strategies used to inspect a scene. Yarbus used contact lenses with small mirrors on them (see Box A) to document (by the position of a reflected beam) the pattern of eye movements made while subjects examined a variety of objects and scenes. Figure 19.1 shows the direction of a subject's gaze while viewing a picture of Queen Nefertiti. The thin, straight lines represent the quick, ballistic eye movements (saccades) used to align the foveas with particular parts of the scene; the denser spots along these lines represent points of fixation where the observer paused for a variable period to take in visual information (little or no visual perception occurs during a saccade, which occupies only a few tens of milliseconds). The results obtained by Yarbus, and subsequently many others, showed that vision is an active process in which eye movements typically shift the view several times each second to selected parts of the scene to examine especially interesting features. The spatial distribution of the fixation points indicates that much more time is spent scrutinizing Nefertiti's eye, nose, mouth, and ear than examining the middle of her cheek or neck. Thus, eye movements allow us to scan the visual field, pausing to focus attention on the portions of the scene that convey the most significant

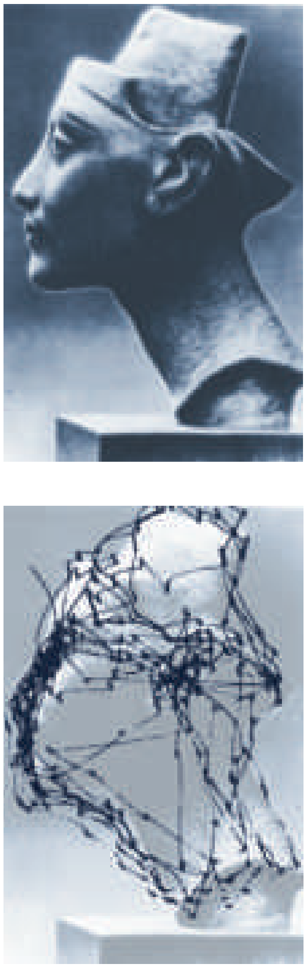


Figure 19.1 The eye movements of a subject viewing a picture of Queen Nefertiti. The bust at the top is what the subject saw; the diagram on the bottom shows the subject's eye movements over a 2–minute viewing period. (From Yarbus, 1967.)

information. As is apparent in Figure 19.1, tracking eye movements can be used to determine what aspects of a scene are particularly arresting. Advertisers now use modern versions of Yarbus' method to determine which pictures and scene arrangements will best sell their product.

The importance of eye movements for visual perception has also been demonstrated by experiments in which a visual image is stabilized on the retina, either by paralyzing the extraocular eye muscles or by moving a scene in exact register with eye movements so that the different features of the image always fall on exactly the same parts of the retina (Box A). Stabilized visual images rapidly disappear, for reasons that remain poorly understood. Nonetheless, these observations on motionless images make it plain that eye movements are also essential for normal visual perception.

The Actions and Innervation of Extraocular Muscles

Three antagonistic pairs of muscles control eye movements: the **lateral** and **medial rectus muscles**, the **superior** and **inferior rectus muscles**, and the **superior** and **inferior oblique muscles**. These muscles are responsible for movements of the eye along three different axes: *horizontal*, either toward the nose (adduction) or away from the nose (abduction); *vertical*, either elevation or depression; and *torsional*, movements that bring the top of the eye toward the nose (intorsion) or away from the nose (extorsion). Horizontal movements are controlled entirely by the medial and lateral rectus muscles; the medial rectus muscle is responsible for adduction, the lateral rectus muscle for abduction. Vertical movements require the coordinated action of the superior and inferior rectus muscles, as well as the oblique muscles. The relative contribution of the rectus and oblique groups depends on the horizontal position of the eye (Figure 19.2). In the primary position (eyes straight ahead), both of these groups contribute to vertical movements. Elevation is due to the action of the superior rectus and inferior oblique muscles, while depression is due to the action of the inferior rectus and superior oblique muscles. When the eye is abducted, the rectus muscles are the prime vertical movers. Elevation is due to the action of the superior rectus, and depression is due to the action of the inferior rectus. When the eye is adducted, the oblique muscles are the prime vertical movers. Elevation is due to the action of the inferior oblique muscle, while depression is due to the action of the superior oblique muscle. The oblique muscles are also primarily responsible for torsional movements.

The extraocular muscles are innervated by lower motor neurons that form three cranial nerves: the abducens, the trochlear, and the oculomotor (Figure 19.3). The **abducens nerve** (cranial nerve VI) exits the brainstem from the pons–medullary junction and innervates the lateral rectus muscle. The **trochlear nerve** (cranial nerve IV) exits from the caudal portion of the midbrain and supplies the superior oblique muscle. In distinction to all other cranial nerves, the trochlear nerve exits from the dorsal surface of the brainstem and crosses the midline to innervate the superior oblique muscle on the contralateral side. The **oculomotor nerve** (cranial nerve III), which exits from the rostral midbrain near the cerebral peduncle, supplies all the rest of the extraocular muscles. Although the oculomotor nerve governs several different muscles, each receives its innervation from a separate group of lower motor neurons within the third nerve nucleus.

In addition to supplying the extraocular muscles, a distinct cell group within the oculomotor nucleus innervates the levator muscles of the eyelid; the axons from these neurons also travel in the third nerve. Finally, the third

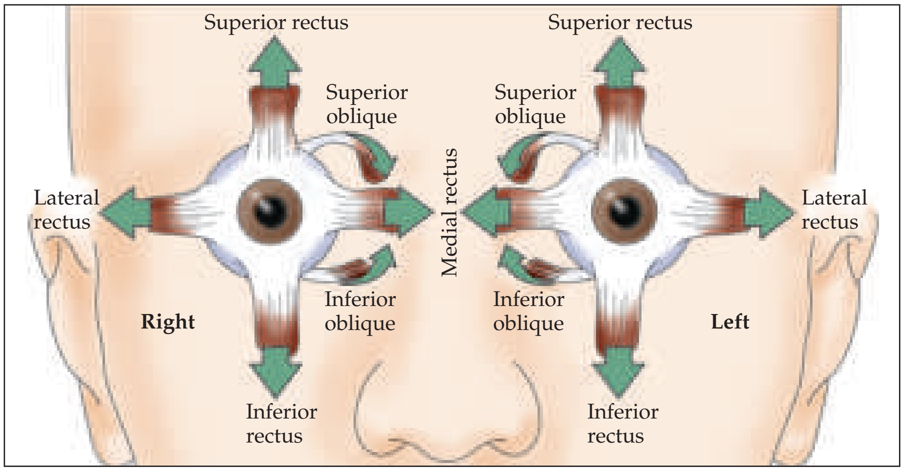
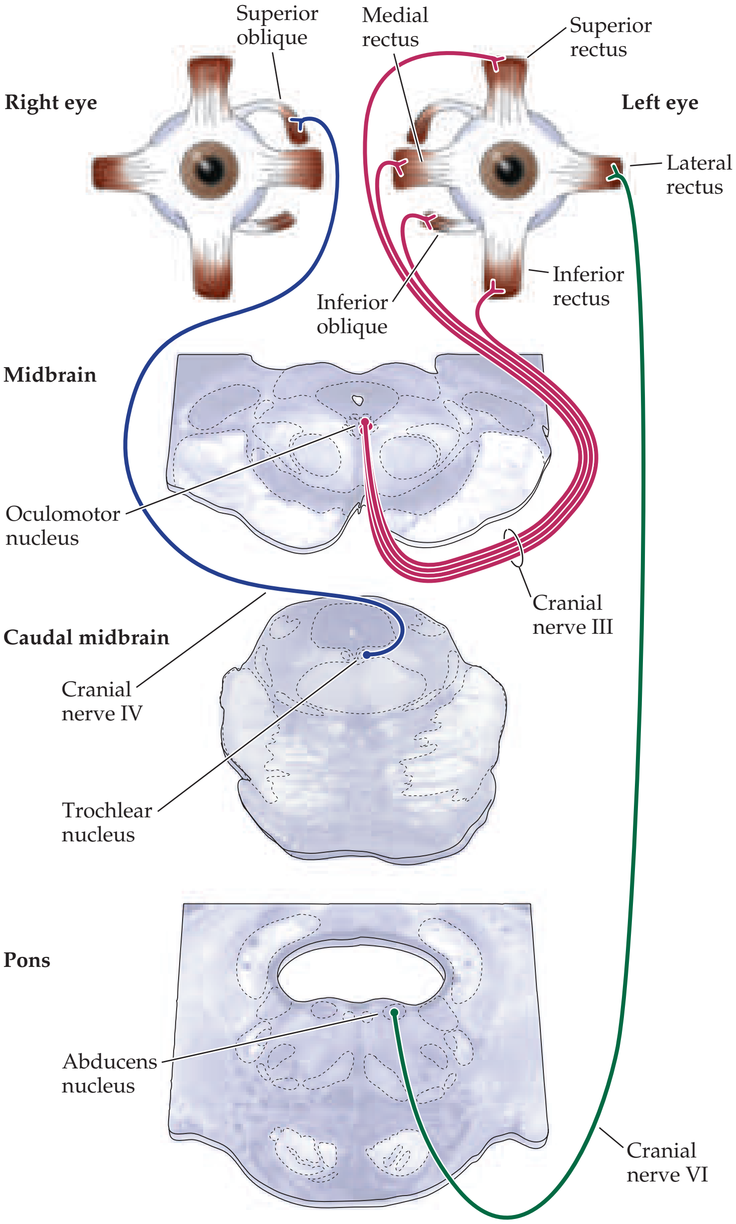

Superior rectus
Superior rectus
Superior oblique
Superior oblique
Lateral rectus
Medial rectus
Lateral rectus
Inferior oblique
Inferior oblique
Right
Left
Inferior rectus
Inferior rectus

Figure 19.2 The contributions of the six extraocular muscles to vertical and horizontal eye movements. Horizontal movements are mediated by the medial and lateral rectus muscles, while vertical movements are mediated by the superior and inferior rectus and the superior and inferior oblique muscle groups.


Superior oblique
Medial rectus
Superior rectus
Right eye
Left eye
Lateral rectus
Inferior rectus
Inferior oblique
Midbrain
Oculomotor nucleus
Cranial nerve III
Caudal midbrain
Cranial nerve IV
Trochlear nucleus
Pons
Abducens nucleus
Cranial nerve VI

sylvius

Figure 19.3 Organization of the cranial nerve nuclei that govern eye movements, showing their innervation of the extraocular muscles. The abducens nucleus innervates the lateral rectus muscle; the trochlear nucleus innervates the superior oblique muscle; and the oculomotor nucleus innervates all the rest of the extraocular muscles (the medial rectus, inferior rectus, superior rectus, and inferior oblique).

Box A

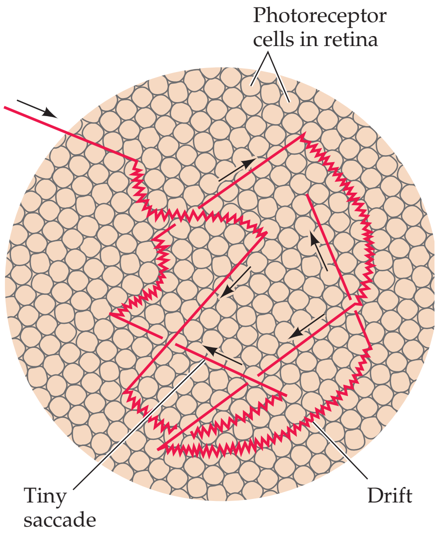
The Perception of Stabilized Retinal Images

Visual perception depends critically on frequent changes of scene. Normally, our view of the world is changed by saccades, and tiny saccades that continue to move the eyes abruptly over a fraction of a degree of visual arc occur even when the observer stares intently at an object of interest. Moreover, continual drift of the eyes during fixation progressively shifts the image onto a nearby but different set of photoreceptors. As a consequence of these several sorts of eye movements (Figure A), our point of view changes more or less continually.

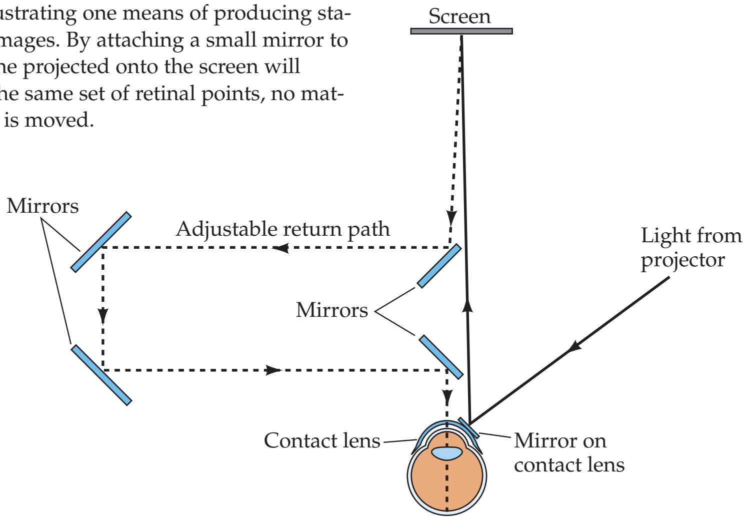
The importance of a continually changing scene for normal vision is dramatically revealed when the retinal image is stabilized. If a small mirror is attached to the eye by means of a contact lens and an image reflected off the mirror onto a screen, then the subject necessarily sees the same thing, whatever the position of the eye: Every time the eye moves, the projected image moves exactly the same amount (Figure B). Under these circumstances, the stabilized image actually disappears from perception within a few seconds!

A simple way to demonstrate the rapid disappearance of a stabilized retinal image is to visualize one's own retinal blood vessels. The blood vessels, which lie in front of the photoreceptor layer, cast a shadow on the underlying receptors. Although normally invisible, the vascular shadows can be seen by moving a source of light across the eye, a phenomenon first noted by J. E. Purkinje more than 150 years ago. This perception can be elicited with an ordinary penlight pressed gently against the lateral side of the closed eyelid. When the light is wiggled vigorously, a rich network of black blood vessel shadows appears against an orange background. (The vessels appear black because they are shadows.) By starting and stopping the movement, it is readily apparent that the image of the blood vessel shadows disappears within a fraction of a second after the light source is stilled.

The conventional interpretation of the rapid disappearance of stabilized images is retinal adaptation. In fact, the phenomenon is at least partly of central origin. Stabilizing the retinal image in one eye, for example, diminishes perception through the other eye, an effect known as interocular transfer. Although the explanation of these remarkable effects is not entirely clear, they emphasize the point that the visual system is designed to deal with novelty.



A) Diagram of the types of eye movements that continually change the retinal stimulus during fixation. The straight lines indicate microsaccades and the curved lines drift; the structures in the background are photoreceptors drawn approximately to scale. The normal scanning movements of the eyes (saccades) are much too large to be shown here, but obviously contribute to the changes of view that we continually experience, as do slow tracking eye movements (although the fovea tracks a particular object, the scene nonetheless changes). (After Pritchard, 1961.)



(B) Diagram illustrating one means of producing stabilized retinal images. By attaching a small mirror to the eye, the scene projected onto the screen will always fall on the same set of retinal points, no matter how the eye is moved.

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nerve carries axons that are responsible for pupillary constriction (see Chapter 11) from the nearby Edinger-Westphal nucleus. Thus, damage to the third nerve results in three characteristic deficits: impairment of eye movements, drooping of the eyelid (ptosis), and pupillary dilation.

Types of Eye Movements and Their Functions

There are four basic types of eye movements: saccades, smooth pursuit movements, vergence movements, and vestibulo-ocular movements. The functions of each type of eye movement are introduced here; in subsequent sections, the neural circuitry responsible for three of these types of movements is presented in more detail (see Chapters 13 and 18 for further discussion of neural circuitry underlying vestibulo-ocular movements).

Saccades are rapid, ballistic movements of the eyes that abruptly change the point of fixation. They range in amplitude from the small movements made while reading, for example, to the much larger movements made while gazing around a room. Saccades can be elicited voluntarily, but occur reflexively whenever the eyes are open, even when fixated on a target (see Box A). The rapid eye movements that occur during an important phase of sleep (see Chapter 27) are also saccades. The time course of a saccadic eye movement is shown in Figure 19.4. After the onset of a target for a saccade (in this example, the stimulus was the movement of an already fixated target), it takes about 200 milliseconds for eye movement to begin. During this delay, the position of the target with respect to the fovea is computed (that is, how far the eye has to move), and the difference between the initial and intended position, or "motor error" (see Chapter 18), is converted into a motor command that activates the extraocular muscles to move the eyes the correct distance in the appropriate direction. Saccadic eye movements are said to be ballistic because the saccade-generating system cannot respond to subsequent changes in the position of the target during the course of the eye movement. If the target moves again during this time (which is on the order of 15–100 ms), the saccade will miss the target, and a second saccade must be made to correct the error.

Smooth pursuit movements are much slower tracking movements of the eyes designed to keep a moving stimulus on the fovea. Such movements are under voluntary control in the sense that the observer can choose whether or not to track a moving stimulus (Figure 19.5). (Saccades can also be voluntary, but are also made unconsciously.) Surprisingly, however, only highly trained observers can make a smooth pursuit movement in the *absence* of a moving target. Most people who try to move their eyes in a smooth fashion without a moving target simply make a saccade.

The smooth pursuit system can be tested by placing a subject inside a rotating cylinder with vertical stripes. (In practice, the subject is more often seated in front of a screen on which a series of horizontally moving vertical bars is presented to conduct this "optokinetic test.") The eyes automatically follow a stripe until they reach the end of their excursion. There is then a quick saccade in the direction opposite to the movement, followed once again by smooth pursuit of a stripe. This alternating slow and fast movement of the eyes in response to such stimuli is called **optokinetic nystagmus**. Optokinetic nystagmus is a normal reflexive response of the eyes in response to large-scale movements of the visual scene and should not be confused with the pathological nystagmus that can result from certain kinds of brain injury (for example, damage to the vestibular system or the cerebellum; see Chapters 13 and 18).

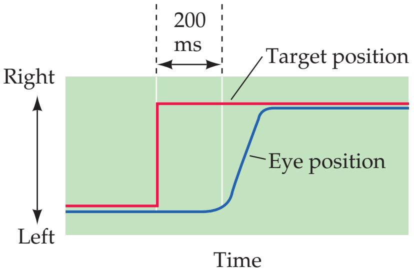


Figure 19.4 The metrics of a saccadic eye movement. The red line indicates the position of a fixation target and the blue line the position of the fovea. When the target moves suddenly to the right, there is a delay of about 200 ms before the eye begins to move to the new target position. (After Fuchs, 1967.)

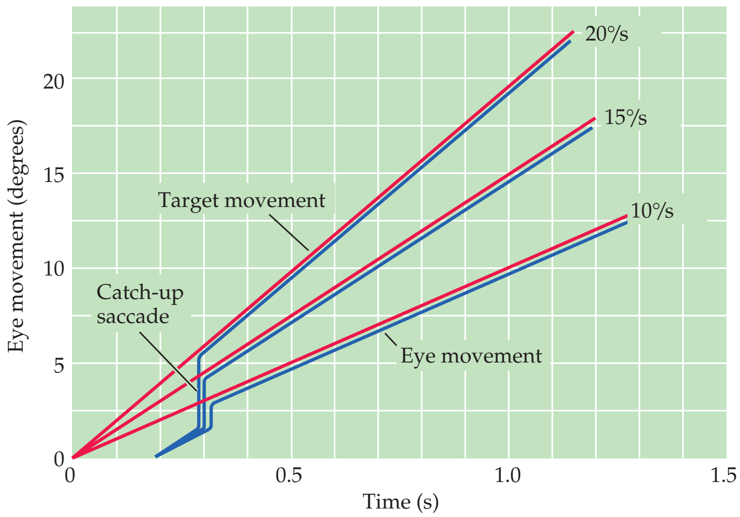


Figure 19.5 The metrics of smooth pursuit eye movements. These traces show eye movements (blue lines) tracking a stimulus moving at three different velocities (red lines). After a quick saccade to capture the target, the eye movement attains a velocity that matches the velocity of the target. (After Fuchs, 1967.)

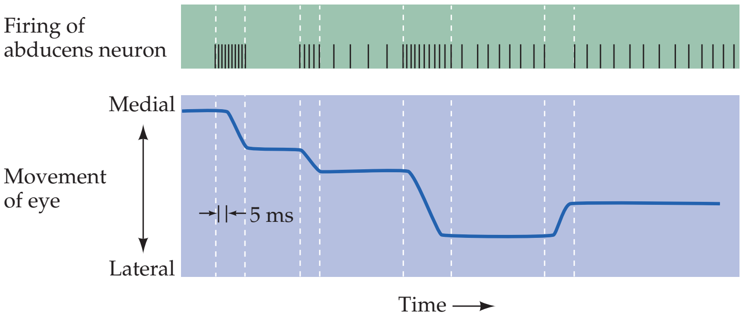
Vergence movements align the fovea of each eye with targets located at different distances from the observer. Unlike other types of eye movements in which the two eyes move in the same direction (**conjugate eye movements**), vergence movements are **disconjugate** (or **disjunctive**); they involve either a convergence or divergence of the lines of sight of each eye to see an object that is nearer or farther away. Convergence is one of the three reflexive visual responses elicited by interest in a near object. The other components of the so-called **near reflex triad** are accommodation of the lens, which brings the object into focus, and pupillary constriction, which increases the depth of field and sharpens the image on the retina (see Chapter 10).

Vestibulo-ocular movements stabilize the eyes relative to the external world, thus compensating for head movements. These reflex responses prevent visual images from "slipping" on the surface of the retina as head position varies. The action of vestibulo-ocular movements can be appreciated by fixating an object and moving the head from side to side; the eyes automatically compensate for the head movement by moving the same distance but in the opposite direction, thus keeping the image of the object at more or less the same place on the retina. The vestibular system detects brief, transient changes in head position and produces rapid corrective eye movements (see Chapter 13). Sensory information from the semicircular canals directs the eyes to move in a direction opposite to the head movement.

Although the vestibular system operates effectively to counteract rapid movements of the head, it is relatively insensitive to slow movements or to persistent rotation of the head. For example, if the vestibulo-ocular reflex is tested with continuous rotation and without visual cues about the movement of the image (i.e.,with eyes closed or in the dark), the compensatory eye movements cease after only about 30 seconds of rotation. However, if the same test is performed with visual cues, eye movements persist. The compensatory eye movements in this case are due to the activation of the smooth pursuit system, which relies not on vestibular information but on visual cues indicating motion of the visual field.

Neural Control of Saccadic Eye Movements

The problem of moving the eyes to fixate a new target in space (or indeed any other movement) entails two separate issues: controlling the *amplitude* of



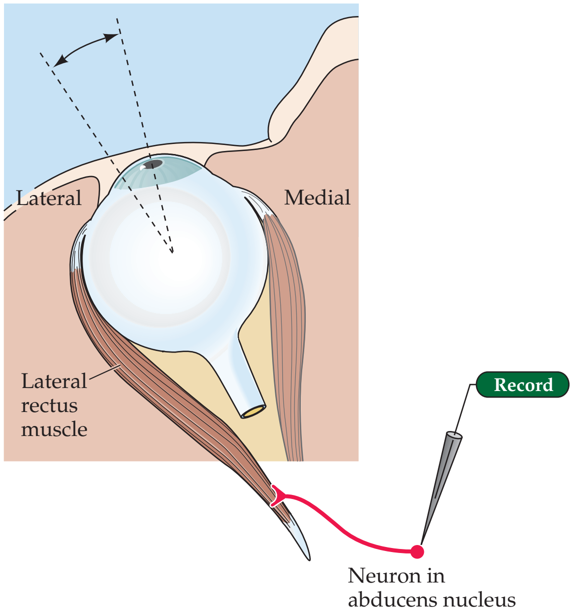


Figure 19.6 Motor neuron activity in relation to saccadic eye movements. The experimental setup is shown on the right. In this example, an abducens lower motor neuron fires a burst of activity (upper trace) that precedes and extends throughout the movement (solid line). An increase in the tonic level of firing is associated with more lateral displacement of the eye. Note also the decline in firing rate during a saccade in the opposite direction. (After Fuchs and Luschei, 1970.)

movement (how far), and controlling the *direction* of the movement (which way). The amplitude of a saccadic eye movement is encoded by the duration of neuronal activity in the lower motor neurons of the oculomotor nuclei. As shown in Figure 19.6, for instance, neurons in the abducens nucleus fire a burst of action potentials prior to abducting the eye (by causing the lateral rectus muscle to contract) and are silent when the eye is adducted. The amplitude of the movement is correlated with the duration of the burst of action potentials in the abducens neuron. With each saccade, the abducens neurons reach a new baseline level of discharge that is correlated with the position of the eye in the orbit. The steady baseline level of firing holds the eye in its new position.

The direction of the movement is determined by which eye muscles are activated. Although in principle any given direction of movement could be specified by independently adjusting the activity of individual eye muscles, the complexity of the task would be overwhelming. Instead, the direction of eye movement is controlled by the local circuit neurons in two **gaze centers** in the reticular formation, each of which is responsible for generating movements along a particular axis. The **paramedian pontine reticular formation** (**PPRF**) or **horizontal gaze center** is a collection of local circuit neurons near the midline in the pons responsible for generating horizontal eye movements (Figure 19.7). The **rostral interstitial nucleus** or **vertical gaze center** is located in the rostral part of the midbrain reticular formation and is responsible for vertical movements. Activation of each gaze center separately results in movements of the eyes along a single axis, either horizontal or vertical. Activation of the gaze centers in concert results in oblique movements whose trajectories are specified by the relative contribution of each center.

An example of how the PPRF works with the abducens and oculomotor nuclei to generate a horizontal saccade to the right is shown in Figure 19.7. Neurons in the PPRF innervate cells in the abducens nucleus on the same side of the brain. There are, however, two types of neurons in the abducens nucleus. One type is a lower motor neuron that innervates the lateral rectus

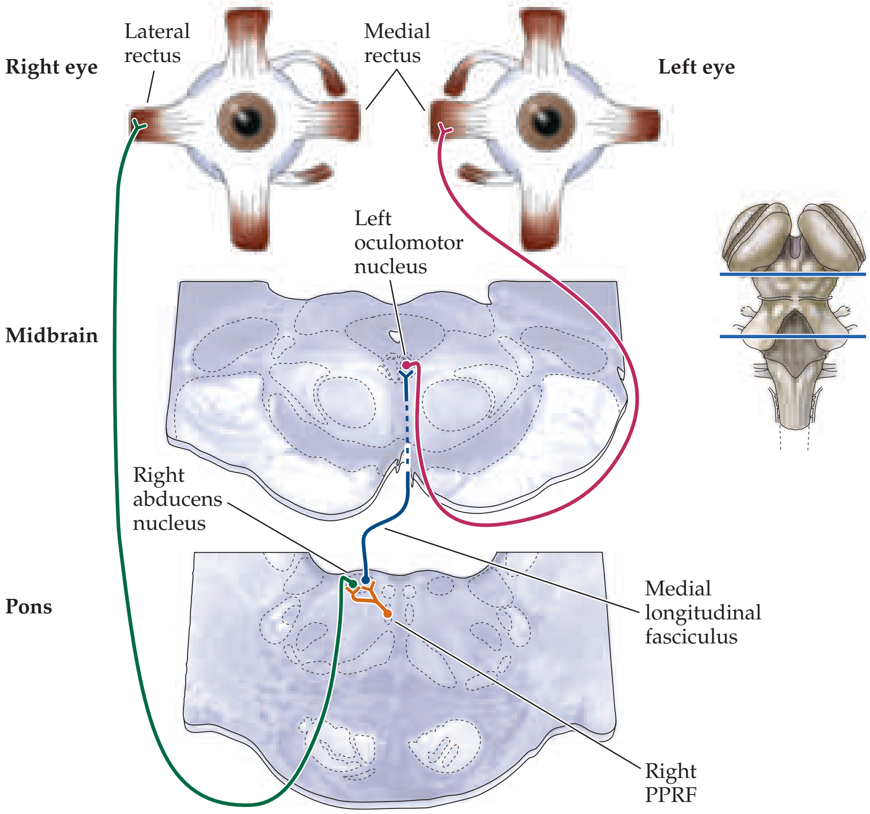


Figure 19.7 Simplified diagram of synaptic circuitry responsible for horizontal movements of the eyes to the right. Activation of local circuit neurons in the right horizontal gaze center (the PPRF; orange) leads to increased activity of lower motor neurons (red and green) and internuclear neurons (blue) in the right abducens nucleus. The lower motor neurons innervate the lateral rectus muscle of the right eye. The internuclear neurons innervate lower motor neurons in the contralateral oculomotor nucleus, which in turn innervate the medial rectus muscle of the left eye.

muscle on the same side. The other type, called internuclear neurons, send their axons across the midline and ascend in a fiber tract called the **medial longitudinal fasciculus**, terminating in the portion of the oculomotor nucleus that contains lower motor neurons innervating the medial rectus muscle. As a result of this arrangement, activation of PPRF neurons on the right side of the brainstem causes horizontal movements of both eyes to the right; the converse is of course true for the PPRF neurons in the left half of the brainstem.

Neurons in the PPRF also send axons to the medullary reticular formation, where they contact inhibitory local circuit neurons. These local circuit neurons, in turn, project to the contralateral abducens nucleus, where they terminate on lower motor neurons and internuclear neurons. In consequence, activation of neurons in the PPRF on the right results in a reduction in the activity of the lower motor neurons whose muscles would oppose movements of the eyes to the right. This inhibition of antagonists resembles the strategy used by local circuit neurons in the spinal cord to control limb muscle antagonists (see Chapter 15).

Although saccades can occur in complete darkness, they are often elicited when something attracts attention and the observer directs the foveas toward the stimulus. How then is sensory information about the location of a target in space transformed into an appropriate pattern of activity in the horizontal and vertical gaze centers? Two structures that project to the gaze centers are demonstrably important for the initiation and accurate targeting of saccadic eye movements: the **superior colliculus** of the midbrain, and a region of the frontal lobe that lies just rostral to premotor cortex, known as the **frontal eye field** (**Brodmann's area 8**). Upper motor neurons in both of these structures, each of which contains a topographical motor map, discharge immediately prior to saccades. Thus, activation of a particular site in the superior colliculus or in the frontal eye field produces saccadic eye movements in a specified direction and for a specified distance that is independent of the initial position of the eyes in the orbit. The direction and distance are always the same for a given stimulation site, changing systematically when different sites are activated.

Both the superior colliculus and the frontal eye field also contain cells that respond to visual stimuli; however, the relation between the sensory and motor responses of individual cells is better understood for the superior colliculus. An orderly map of visual space is established by the termination of retinal axons within the superior colliculus (see Chapter 11), and this sensory map is in register with the motor map that generates eye movements. Thus, neurons in a particular region of the superior colliculus are activated by the presentation of visual stimuli in a limited region of visual space. This activation leads to the generation of a saccade that moves the eye by an amount just sufficient to align the foveas with the region of visual space that provided the stimulation (Figure 19.8).

Neurons in the superior colliculus also respond to auditory and somatic stimuli. Indeed, the location in space for these other modalities also is mapped in register with the motor map in the colliculus. Topographically organized maps of auditory space and of the body surface in the superior colliculus can therefore orient the eyes (and the head) in response to a variety of different sensory stimuli. This registration of the sensory and motor maps in the colliculus illustrates an important principle of topographical maps in the motor system, namely to provide an efficient mechanism for sensory motor transformations (Box B).

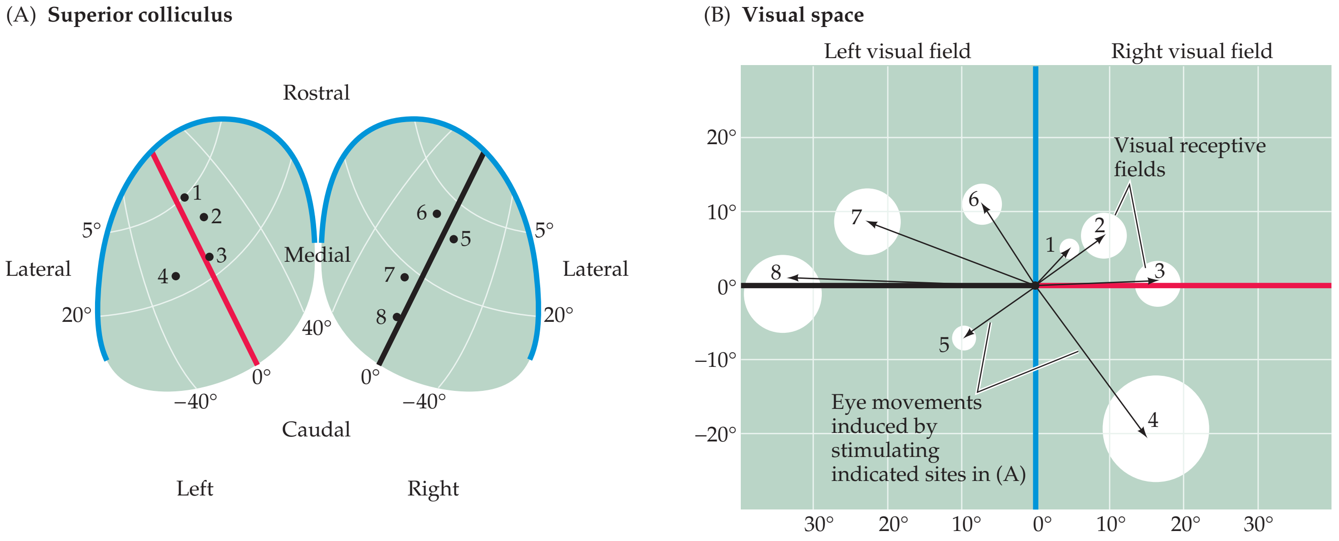


Figure 19.8 Evidence for sensory motor transformation obtained from electrical recording and stimulation in the superior colliculus. (A) Surface views of the superior colliculus illustrating the location of eight separate electrode recording and stimulation sites. (B) Map of visual space showing the receptive field location of the sites in (A) (white circles), and the amplitude and direction of the eye movements elicited by stimulating these sites electrically (arrows). In each case, electrical stimulation results in eye movements that align the fovea with a region of visual space that corresponds to the visual receptive field of the site. (After Schiller and Stryker, 1972.)

Box B

Sensory Motor Integration in the Superior Colliculus

The superior colliculus is a laminated structure in which the differences between the layers provide clues about how sensory and motor maps interact to produce appropriate movements. As discussed in the text, the superficial or "visual" layer of the colliculus receives input from retinal axons that form a topographic map. Thus, each site in the superficial layer is activated maximally by the presence of a stimulus at a particular point of visual space. In contrast, neurons in the deeper or "motor" layers generate bursts of action potentials that command saccades, effectively generating a motor map; thus, activation of different sites generates saccades having different vectors. The visual and motor maps are *in register*, so that visual cells responding to a stimulus in a specific region of visual space are located directly above the motor cells that command eye movements toward that same region (see Figure 19.8).

The registration of the visual and motor maps suggests a simple strategy for how the eyes might be guided toward an object of interest in the visual field. When an object appears at a particular location in the visual field, it will activate neurons in the corresponding part of the visual map. As a result, bursts of action potentials are generated by the subjacent motor cells to command a saccade that rotates the two eyes just the right amount to direct the foveas toward that same location in the visual field. This behavior is called "visual grasp" because successful sensory motor integration results in the accurate foveation of a visual target.

This seemingly simple model, formulated in the early 1970s when the collicular maps were first found, assumes point to point connections between the visual and motor maps. In practice, however, these connections have been difficult to demonstrate. Neither the anatomical nor the physiological methods available at the time were sufficiently precise to establish these postulated synaptic connections. At about the same time, motor neurons were found to command saccades to nonvisual stimuli; moreover, spontaneous saccades occur in the dark. Thus, it was clear that visual layer activity is not always necessary for saccades. To confuse matters further, animals could be trained *not* to make a saccade when an object appeared in the visual field, showing that the activation of visual neurons is sometimes insufficient to command saccades. The fact that activity of neurons in the visual map is *neither necessary nor sufficient* for eliciting saccades led investigators away from the simple model of direct connections between corresponding regions of the two maps, toward models that linked the layers indirectly through pathways that detoured through the cortex.

Eventually, however, new and better methods resolved this uncertainty. Techniques for filling single cells with axonal tracers showed an overlap between descending visual layer axons and ascending motor layer dendrites, in accord with direct anatomical connections between corresponding regions of the maps. At the same time, in vitro whole-cell patch clamp recording (see Box A in Chapter 4) permitted more discriminating functional studies that distinguished excitatory and inhibitory inputs to the motor cells. These experiments showed that the visual and motor layers do indeed have the functional connections required to initiate the command for a visually guided saccadic eye movement. A single brief electrical stimulus delivered to the superficial layer generates a prolonged burst of action potentials that resembles the command bursts that normally occur just before a saccade (see figure).

These direct connections presumably provide the substrate for the very short latency reflex-like "express saccades" that are unaffected by destruction of the frontal eye fields. Other visual and nonvisual inputs to the deep layers probably explain why activation of the retina is neither necessary nor sufficient for the production of saccades.

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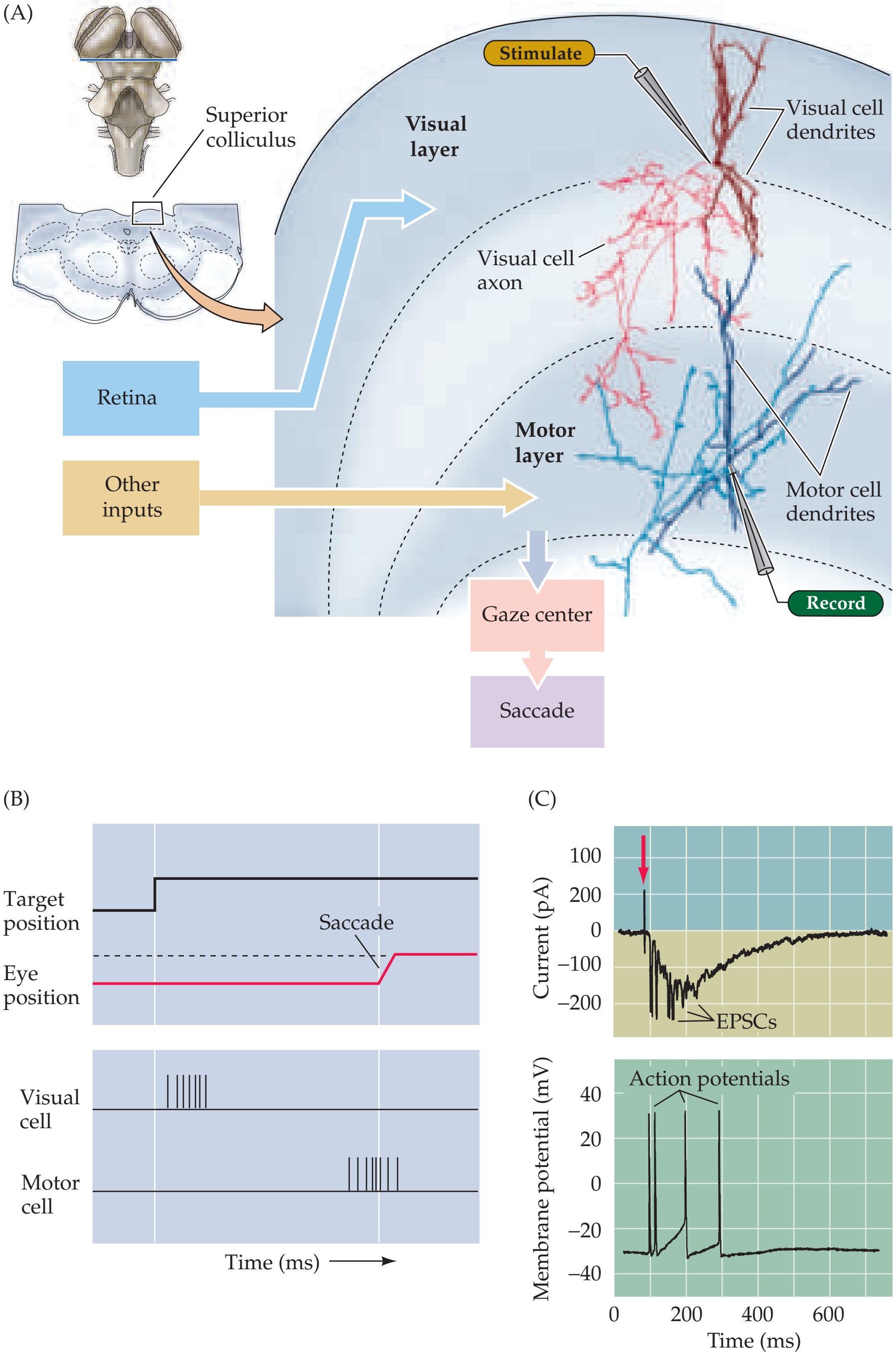
The functional relationship between the frontal eye field and the superior colliculus in controlling eye movements is similar to that between the motor cortex and the red nucleus in the control of limb movements (see Chapter 16). The frontal eye field projects to the superior colliculus, and the superior colliculus projects to the PPRF on the contralateral side (Figure 19.9). (It also projects to the vertical gaze center, but for simplicity the discussion here is


(A)
Superior colliculus
Visual layer
Stimulate
Visual cell dendrites
Visual cell axon
Retina
Other inputs
Motor layer
Motor cell dendrites
Record
Gaze center
Saccade
(B)
Target position
Eye position
Saccade
Visual cell
Motor cell
Time (ms)
(C)
100
200
0
−100
−200
Current (pA)
EPSCs
Action potentials
40
20
0
−20
−40
Membrane potential (mV)
0
200
400
600
Time (ms)

(A) The superior colliculus receives visual input from the retina and sends a command signal to the gaze centers to initiate a saccade (see text). In the experiment illustrated here, a stimulating electrode activates cells in the visual layer and a patch clamp pipette records the response evoked in a neuron in the subjacent motor layer. The cells in the visual and motor layers were subsequently labeled with a tracer called biocytin. This experiment demonstrates that the terminals of the visual neuron are located in the same region as the dendrites of the motor neuron. (B) The onset of a target in the visual field (top trace) is followed after a short interval by a saccade to foveate the target (second trace). In the superior colliculus, the visual cell responds shortly after the onset of the target, while the motor cell responds later, just before the onset of the saccade. (C) Bursts of excitatory postsynaptic currents (EPSCs) recorded from a motor layer neuron in response to a brief (0.5 ms) current stimulus applied via a steel wire electrode in the visual layer (top; see arrow). These synaptic currents generate bursts of action potentials in the same cell (bottom). (B after Wurtz and Albano, 1980; C after Ozen et al., 2000.)

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limited to the PPRF.) The frontal eye field can thus control eye movements by activating selected populations of superior colliculus neurons. This cortical area also projects directly to the contralateral PPRF; as a result, the frontal eye field can also control eye movements independently of the superior colliculus. The parallel inputs to the PPRF from the frontal eye field and superior colliculus are reflected in the deficits that result from damage to these

Figure 19.9 The relationship of the frontal eye field in the right cerebral hemisphere (Brodmann's area 8) to the superior colliculus and the horizontal gaze center (PPRF). There are two routes by which the frontal eye field can influence eye movements in humans: indirectly by projections to the superior colliculus, which in turn projects to the contralateral PPRF, and directly by projections to the contralateral PPRF.

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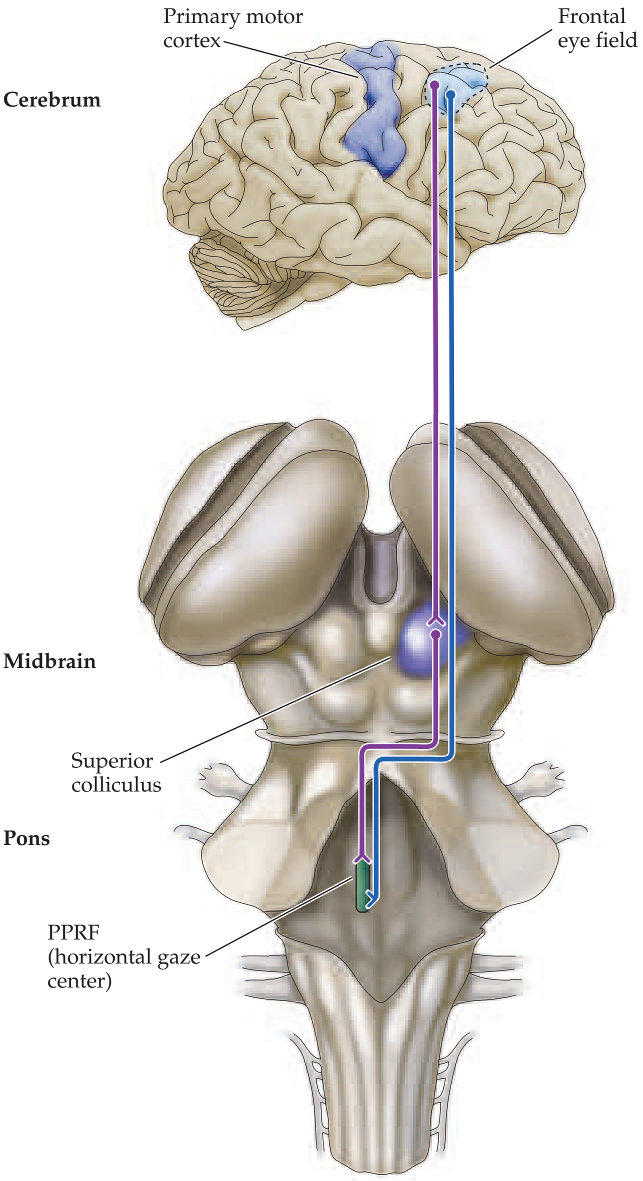
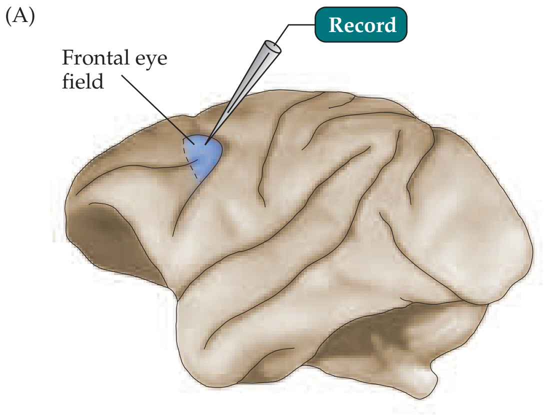


structures. Injury to the frontal eye field results in an inability to make saccades to the contralateral side and a deviation of the eyes to the side of the lesion. These effects are transient, however; in monkeys with experimentally induced lesions of this cortical region, recovery is virtually complete in two to four weeks. Lesions of the superior colliculus change the accuracy, frequency, and velocity of saccades; yet saccades still occur, and the deficits also improve with time. These results suggest that the frontal eye fields and the superior colliculus provide complementary pathways for the control of saccades. Moreover, one of these structures appears to be able to compensate (at least partially) for the loss of the other. In support of this interpretation, combined lesions of the frontal eye field and the superior colliculus produce a dramatic and permanent loss in the ability to make saccadic eye movements.

These observations do not, however, imply that the frontal eye fields and the superior colliculus have the same functions. Superior colliculus lesions produce a permanent deficit in the ability to perform very short latency reflex-like eye movements called "express saccades." The express saccades are evidently mediated by direct pathways to the superior colliculus from the retina or visual cortex that can access the upper motor neurons in the colliculus without extensive, and more time-consuming, processing in the frontal cortex (see Box B). In contrast, frontal eye field lesions produce permanent deficits in the ability to make saccades that are not guided by an external target. For example, patients (or monkeys) with a lesion in the frontal eye fields cannot voluntarily direct their eyes *away* from a stimulus in the visual field, a type of eye movement called an "antisaccade." Such lesions also eliminate the ability to make a saccade to the remembered location of a target that is no longer visible.

Finally, the frontal eye fields are essential for systematically scanning the visual field to locate an object of interest within an array of distracting objects (see Figure 19.1). Figure 19.10 shows the responses of a frontal eye field neuron during a visual task in which a monkey was required to foveate a target located within an arrray of distracting objects. This frontal eye field



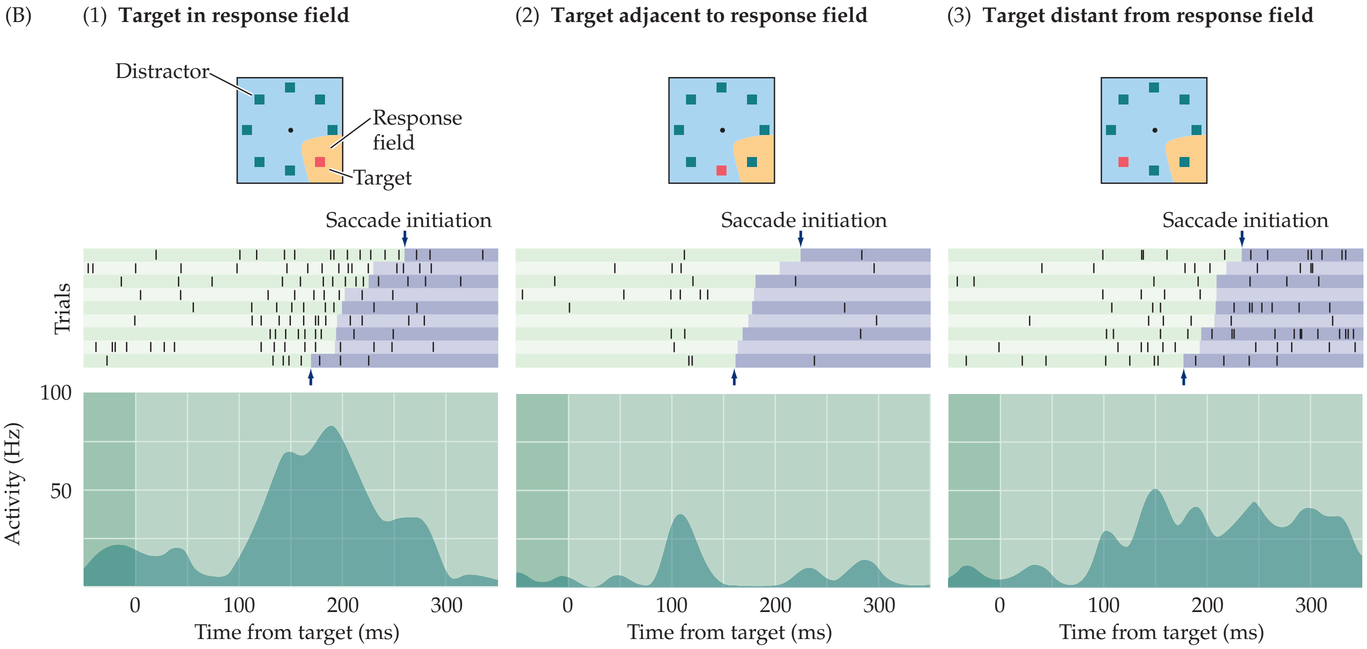


Figure 19.10 Responses of neurons in the frontal eye fields. (A) Locus of the left frontal eye field on a lateral view of the rhesus monkey brain. (B) Activation of a frontal eye field neuron during visual search for a target. The vertical tickmarks represent action potentials, and each row of tick marks is a different trial. The graphs below show the average frequency of action potentials as a function of time. The change in color from green to purple in each row indicates the time of onset of a saccade toward the target. In the left trace (1), the target (red square) is in the part of the visual field "seen" by the neuron, and the response to the target is similar to the response that would be generated by the neuron even if no distractors (green squares) were present (not shown). In the right trace (3), the target is far from the response field of the neuron. The neuron responds to the distractor in its response field. However, it responds at a lower rate than it would to exactly the same stimulus if the square were not a distractor but a target for a saccade (left trace). In the middle trace (2), the response of the neuron to the distractor has been sharply reduced by the presence of the target in a neighboring region of the visual field. (After Schall, 1995.)

neuron discharges at different levels to the same stimulus, depending on whether the stimulus is the target of the saccade or a "distractor," and on the location of the distractor relative to the actual target. For example, the differences between the middle and the left and right traces in Figure 19.10 demonstrate that the response to the distractor is much reduced if it is located close to the target in the visual field. Results such as these suggest that lateral interactions within the frontal eye fields enhance the neuronal responses to stimuli that will be selected as saccade targets, and that such interactions suppress the responses to uninteresting and potentially distracting stimuli. These sorts of interactions presumably reduce the occurrence of unwanted saccades to distracting stimuli in the visual field.

Neural Control of Smooth Pursuit Movements

Smooth pursuit movements are also mediated by neurons in the PPRF, but are under the influence of motor control centers other than the superior colliculus and frontal eye field. (The superior colliculus and frontal eye field are exclusively involved in the generation of saccades.) The exact route by which visual information reaches the PPRF to generate smooth pursuit movements is not known (a pathway through the cerebellum has been suggested). It is clear, however, that neurons in the striate and extrastriate visual areas provide sensory information that is essential for the initiation and accurate guidance of smooth pursuit movements. In monkeys, neurons in the middle temporal area (which is largely concerned with the perception of moving stimuli and a target of the magnocellular stream; see Chapter 11) respond selectively to targets moving in a specific direction. Moreover, damage to this area disrupts smooth pursuit movements. In humans, damage of comparable areas in the parietal and occipital lobes also results in abnormalities of smooth pursuit movements. Unlike the effects of lesions to the frontal eye field and the superior colliculus, the deficits are in eye movements made toward the side of the lesion. For example, a lesion of the left parieto-occipital region is likely to result in an inability to track an object moving from right to left.

Neural Control of Vergence Movements

When a person wishes to look from one object to another object that are located at different distances from the eyes, a saccade is made that shifts the direction of gaze toward the new object, and the eyes either diverge or converge until the object falls on the fovea of each eye. The structures and pathways responsible for mediating the vergence movements are not well understood, but appear to include several extrastriate areas in the occipital lobe (see Chapter 11). Information about the location of retinal activity is relayed through the two lateral geniculate nuclei to the cortex, where the information from the two eyes is integrated. The appropriate command to diverge or converge the eyes, which is based largely on information from the two eyes about the amount of binocular disparity (see Chapter 11), is then sent via upper motor neurons from the occipital cortex to "vergence centers" in the brainstem. One such center is a population of local circuit neurons located in the midbrain near the oculomotor nucleus. These neurons generate a burst of action potentials. The onset of the burst is the command to generate a vergence movement, and the frequency of the burst determines its velocity.

There is a division of labor within the vergence center, so that some neurons command convergence movements while others command divergence movements. These neurons also coordinate vergence movements of the eyes with accommodation of the lens and pupillary constriction to produce the near reflex discussed in Chapter 10.

Summary

Despite their specialized function, the systems that control eye movements have much in common with the motor systems that govern movements of other parts of the body. Just as the spinal cord provides the basic circuitry for coordinating the actions of muscles around a joint, the reticular formation of the pons and midbrain provides the basic circuitry that mediates movements of the eyes. Descending projections from higher-order centers in the superior colliculus and the frontal eye field innervate the brainstem gaze centers, providing a basis for integrating eye movements with a variety of sensory information that indicates the location of objects in space. The superior colliculus and the frontal eye field are organized in a parallel as well as a hierarchical fashion, enabling one of these structures to compensate for the loss of the other. Eye movements, like other movements, are also under the control of the basal ganglia and cerebellum (see Chapters 17 and 18); this control ensures the proper initiation and successful execution of these relatively simple motor behaviors, thus allowing observers to interact efficiently with the universe of things that can be seen.

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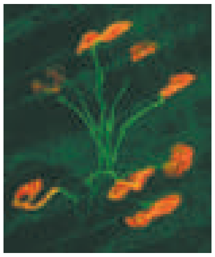
Chapter 20



The Visceral Motor System

Overview

The visceral (or autonomic) motor system controls involuntary functions mediated by the activity of smooth muscle fibers, cardiac muscle fibers, and glands. The system comprises two major divisions, the sympathetic and parasympathetic subsystems (the specialized innervation of the gut provides a further semi-independent division and is usually referred to as the enteric nervous system). Although these divisions are always active at some level, the sympathetic subsystem mobilizes the body's resources for dealing with challenges of one sort or another. Conversely, parasympathetic activity predominates during states of relative quiescence, so that energy sources previously expended can be restored. This continuous neural regulation of the expenditure and replenishment of the body's resources contributes importantly to the overall physiological balance of bodily functions called homeostasis. Whereas the major controlling centers for somatic motor activity are the primary and secondary motor cortices in the frontal lobes and a variety of related subcortical nuclei, the major locus of central control in the visceral motor system is the hypothalamus and the complex (and ill-defined) circuitry that it controls in the brainstem reticular formation and spinal cord. The status of both principal divisions of the visceral motor system is modulated by descending pathways from these centers to preganglionic neurons in the brainstem and spinal cord, which in turn determine the activity of the primary visceral motor neurons in autonomic ganglia. The autonomic regulation of several organ systems of particular importance in clinical practice (including cardiovascular function, control of the bladder, and the governance of the reproductive organs) is considered in more detail as specific examples of visceral motor control.

Early Studies of the Visceral Motor System

Although humans must always have been aware of involuntary motor reactions to stimuli in the environment (e.g., narrowing of the pupil in response to bright light, constriction of superficial blood vessels in response to cold or fear, increased heart rate in response to exertion), it was not until the late nineteenth century that the neural control of these and other visceral functions came to be understood in modern terms. The researchers who first rationalized the workings of the **visceral motor system** were Walter Gaskell and John Langley, two British physiologists at Cambridge University. Gaskell, whose work preceded that of Langley, established the overall anatomy of the system and carried out early physiological experiments that demonstrated some of its salient functional characteristics (e.g., that the heartbeat of an experimental animal is accelerated by stimulating the outflow of the upper thoracic spinal cord segments). Based on these and other observations, Gaskell concluded in 1866 that “every tissue is innervated by two sets of nerve fibers of opposite characters,” and he further surmised that these actions showed “the characteristic signs of opposite chemical processes.”

Using similar electrical stimulation techniques in experimental animals, Langley went on to establish the function of **autonomic ganglia** (which harbor the primary visceral motor neurons), defined the terms “preganglionic” and “postganglionic” (see below), and coined the phrase **autonomic nervous system** (which is commonly used as a synonym for “visceral motor system,” although certain somatic motor activities may also be considered “autonomic”; see Chapter 28). Langley’s work on the pharmacology of the autonomic system initiated the classical studies indicating the roles of acetylcholine and the catecholamines in visceral motor function, and in neurotransmitter function more generally (see Chapter 6). In short, Langley’s ingenious physiological and anatomical experiments established in detail the general proposition put forward by Gaskell on circumstantial grounds.

The third major figure in the pioneering studies of the visceral motor system was Walter Cannon at Harvard Medical School, who during the early to mid-1900s devoted his career to understanding visceral motor functions in relation to homeostatic mechanisms generally, and to the emotions and higher brain functions in particular (see Chapter 28). Like Gaskell and Langley before him, this work was based primarily on electrical stimulation in experimental animals, but included activation of brainstem and other brain regions as well as the peripheral components of the system. He also established the effects of denervation in the visceral motor system, laying some of the basis for much further work on what is now referred to as “neuronal plasticity” (see Chapter 24).

Distinctive Features of the Visceral Motor System

Chapters 15 and 16 discussed in detail the organization of lower motor neurons in the central nervous system, their relationships to striated muscle fibers, and the means by which their activities are governed by higher motor centers. With respect to the efferent systems that govern the actions of smooth muscle fibers, cardiac muscle fibers, and glands, it is instructive to recognize the anatomical and functional features of the visceral motor system that distinguish it from the somatic motor system.

First, although it is useful to recognize medial (postural control) and lateral (distal extremity control) components of the somatic motor system (see Chapters 15 and 16), the anatomical and functional distinctions that justify this division of the somatic motor system are not nearly so great as they are for the three subsystems that comprise the visceral motor system.

Second, the lower motor neurons of the visceral motor system are located outside of the central nervous system; the cell bodies of primary visceral motor neurons are found in autonomic ganglia that are either close to the spinal cord (sympathetic division) or embedded in a neural plexus (*plexus* means “network”) very near or in the target organ (parasympathetic and enteric divisions).

Third, the contacts between visceral motor neurons and target tissues are much less differentiated than the neuromuscular junctions of the somatic motor system. Visceral motor axons tend to be highly branched and give rise to many synaptic terminals at varicosities (swellings) along the length of the terminal axonal branch. Moreover, the surfaces of the target tissue usually lack the highly ordered structure of the motor endplates that characterizes postsynaptic target sites on striated muscle fibers. As a consequence, the neurotransmitters released by visceral motor terminals often diffuse for hundreds of microns before binding to postsynaptic receptors—a far greater distance than at the synaptic cleft of the somatic neuromuscular junction.

Fourth, visceral motor terminals release a variety of neurotransmitters, including primary small-molecule neurotransmitters (which differ depending on whether the motor neuron in question is sympathetic or parasympathetic), and one or more of a variety of co-neurotransmitters that may be a different small-molecule type or a neuropeptide (see Chapter 6). These neurotransmitters in turn interact with a diverse set of postsynaptic receptors that mediate a myriad of postsynaptic effects in the target tissues. It should be clear, then, that while the major effect of somatic motor activation on striated muscle is nearly the same throughout the body, the effects of visceral motor activation are remarkably varied. This fact should come as no surprise, given the challenge of maintaining homeostasis across the many organ systems of the body in the face of variable environmental conditions and dynamic behavioral contingencies.

Finally, whereas the principal actions of the somatic motor system are governed by motor cortical areas in the posterior frontal lobe (discussed in Chapter 16), the activities of the visceral motor system are coordinated by a distributed set of cortical and subcortical structures in the ventral and medial parts of the forebrain; collectively, these structures comprise a central autonomic network.

In the remaining sections of this chapter, the sympathetic and parasympathetic divisions and the enteric nervous system are separately considered. General principles of visceral motor control and the central and reflexive coordination of visceral motor and somatic motor activity are illustrated in more detail later in the chapter, in a discussion of specific autonomic reflexes related to cardiovascular control, urination, and sexual functioning.

The Sympathetic Division of the Visceral Motor System

Activity of the neurons that make up the sympathetic division of the visceral motor system ultimately prepares individuals for “flight or fight,” as Cannon famously put it. Cannon meant that, in extreme circumstances, heightened levels of sympathetic neural activity allow the body to make maximum use of its resources (particularly its metabolic resources), thereby increasing the chances of survival or success in threatening or otherwise challenging situations. Thus, during high levels of sympathetic activity, the pupils dilate and the eyelids retract (allowing more light to reach the retina and the eyes to move more efficiently); the blood vessels of the skin and gut constrict (rerouting blood to muscles, thus allowing them to extract a maximum of available energy); the hairs stand on end (making our hairier ancestors look more fearsome); the bronchi dilate (increasing oxygenation); the heart rate accelerates and the force of cardiac contraction is enhanced (maximally perfusing skeletal muscles and the brain); and digestive and other vegetative functions become quiescent (thus diminishing activities that are temporarily inappropriate) (Figure 20.1). At the same time, sympathetic activity stimulates the adrenal medulla to release epinephrine and norepinephrine into the bloodstream and mediates the release of glucagon and insulin from the pancreas, further enhancing energy mobilizing (or catabolic) functions.

The neurons in the central nervous system that drive these effects are located in the spinal cord. They are arranged in a column of **preganglionic**

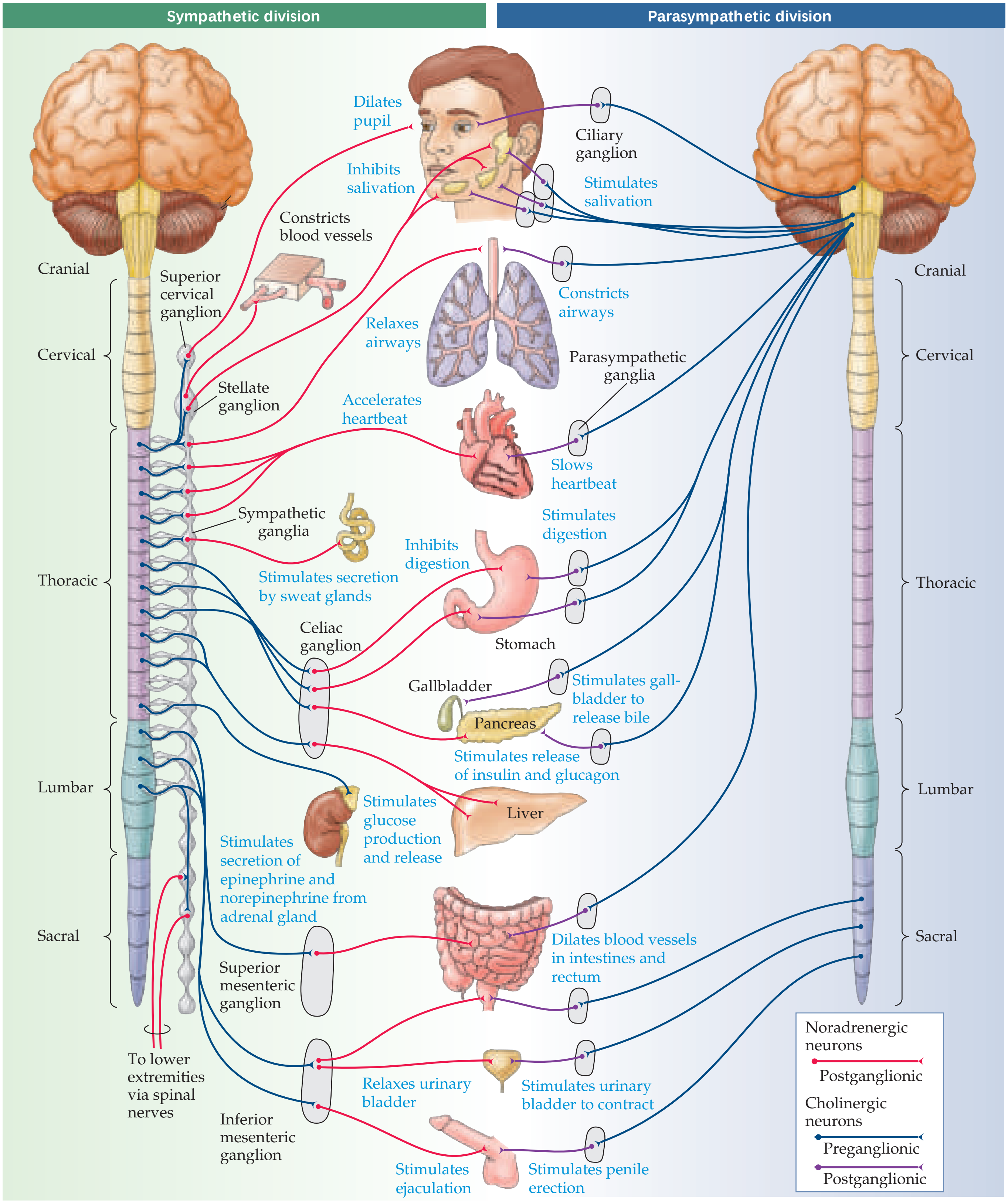

Sympathetic division
Parasympathetic division
Dilates pupil
Inhibits salivation
Constricts blood vessels
Cranial
Superior cervical ganglion
Cervical
Stellate ganglion
Relaxes airways
Accelerates heartbeat
Sympathetic ganglia
Stimulates secretion by sweat glands
Thoracic
Celiac ganglion
Inhibits digestion
Stomach
Gallbladder
Pancreas
Stimulates release of insulin and glucagon
Liver
Stimulates glucose production and release
Lumbar
Stimulates secretion of epinephrine and norepinephrine from adrenal gland
Sacral
Superior mesenteric ganglion
To lower extremities via spinal nerves
Inferior mesenteric ganglion
Relaxes urinary bladder
Stimulates ejaculation
Ciliary ganglion
Stimulates salivation
Constricts airways
Parasympathetic ganglia
Slows heartbeat
Stimulates digestion
Stimulates gallbladder to release bile
Dilates blood vessels in intestines and rectum
Stimulates urinary bladder to contract
Stimulates penile erection
Cranial
Cervical
Thoracic
Lumbar
Sacral
Noradrenergic neurons
Postganglionic
Cholinergic neurons
Preganglionic
Postganglionic

Figure 20.1 Overview of the sympathetic (left side of the figure) and parasympathetic (right side of the figure) divisions of the visceral motor system.

neurons that extends from the uppermost thoracic to the upper lumbar segments (T1 to L2 or L3; Table 20.1) in a region of the spinal cord gray matter called the **intermediolateral column** or **lateral horn** (Figure 20.2). The preganglionic neurons that control sympathetic outflow to the organs in the

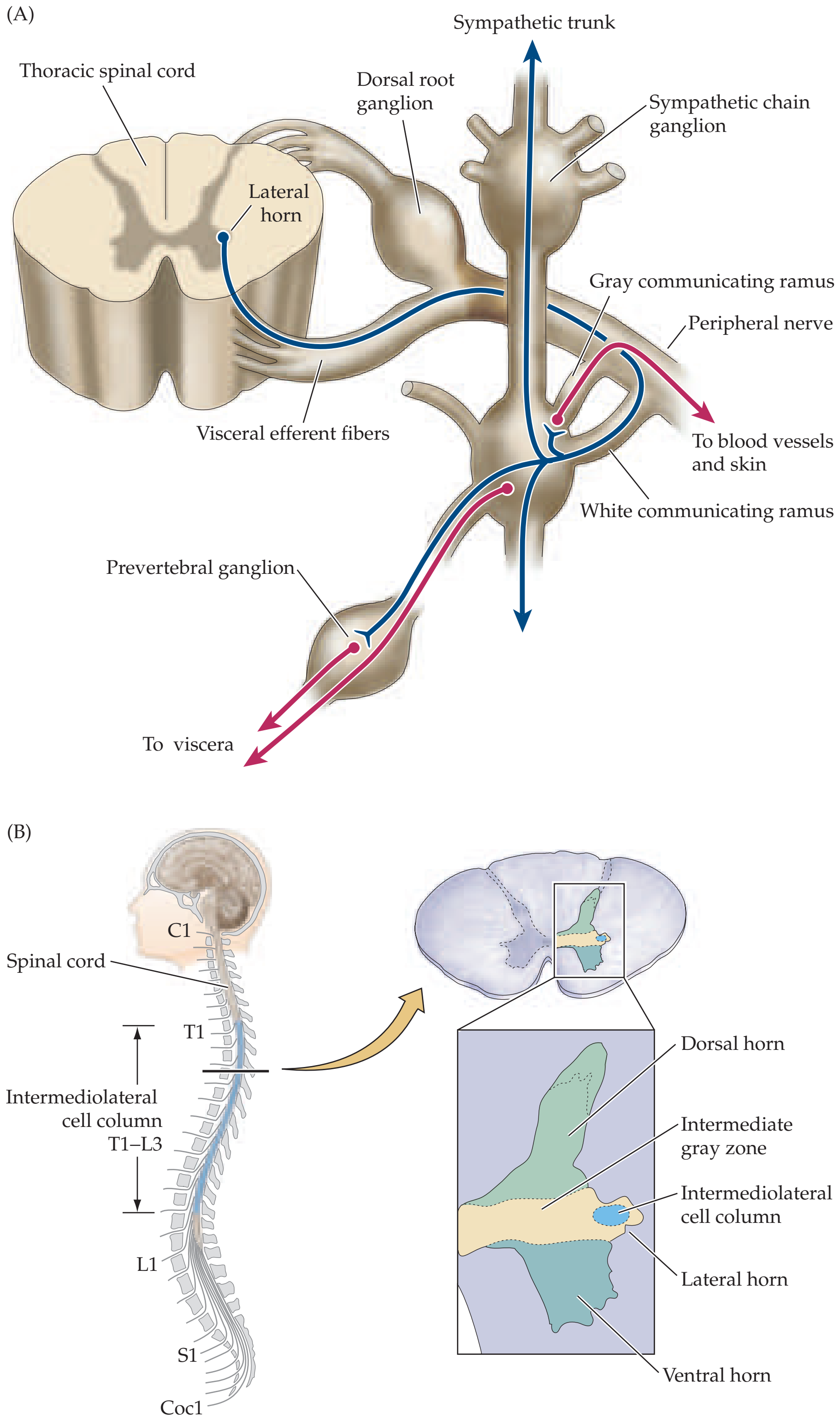

(A)
Sympathetic trunk
Thoracic spinal cord
Dorsal root ganglion
Sympathetic chain ganglion
Lateral horn
Gray communicating ramus
Peripheral nerve
Visceral efferent fibers
To blood vessels and skin
White communicating ramus
Prevertebral ganglion
To viscera
(B)
C1
Spinal cord
T1
Intermediolateral cell column T1–L3
L1
S1
Coc1
Dorsal horn
Intermediate gray zone
Intermediolateral cell column
Lateral horn
Ventral horn

Figure 20.2 Organization of the preganglionic spinal outflow to sympathetic ganglia. (A) General organization of the sympathetic division of the visceral motor system in the spinal cord and the preganglionic outflow to the sympathetic ganglia that contain the primary visceral motor neurons. (B) Cross section of thoracic spinal cord at the level indicated, showing location of the sympathetic preganglionic neurons in the intermediolateral cell column of the lateral horn.

TABLE 20.1

Summary of the Major Functions of the Visceral Motor System

Sympathetic Division			
Target organ	**Location of preganglionic neurons**	**Location of ganglionic neurons**	**Actions**
Eye	Upper thoracic spinal cord (C8–T7)	Superior cervical ganglion	Pupillary dilation
Lacrimal gland			Tearing
Submandibular and sublingual glands			Vasoconstriction
Parotid gland			Vasoconstriction
Head, neck (blood vessels, sweat glands, piloerector muscles)			Sweat secretion, vasoconstriction, piloerection
Upper extremity	T3–T6	Stellate and upper thoracic ganglia	Sweat secretion, vasoconstriction, piloerection
Heart	Middle thoracic spinal cord (T1–T5)	Superior cervical and upper thoracic ganglia	Increased heart rate and stroke volume, dilation of coronary arteries
Bronchi, lungs		Upper thoracic ganglia	Vasodilation, bronchial dilation
Stomach	Lower thoracic spinal cord (T6–T10)	Celiac ganglion	Inhibition of peristaltic movement and gastric secretion, vasoconstriction
Pancreas		Celiac ganglion	Vasoconstriction, insulin secretion
Ascending small intestine, transverse large intestine		Celiac, superior, and inferior mesenteric ganglia	Inhibition of peristaltic movement and secretion
Descending large intestine, sigmoid, rectum		Inferior mesenteric hypogastric, and pelvic plexus	Inhibition of peristaltic movement and secretion
Adrenal gland	T9–L2	Cells of gland are modified neurons	Catecholamine secretion
Ureter, bladder	T11–L2	Hypogastric and pelvic plexus	Relaxation of bladder wall muscle and contraction of internal sphincter
Lower extremity	T10–L2	Lower lumbar and upper sacral ganglia	Sweat secretion, vasoconstriction, piloerection

TABLE 20.1
Summary of the Major Functions of the Visceral Motor System (*continued*)

Parasympathetic Division			
Target organ	**Location of preganglionic neurons**	**Location of ganglionic neurons**	**Actions**
Eye	Edinger-Westphal nucleus	Ciliary ganglion	Pupillary constriction, accommodation
Lacrimal gland	Superior salivatory nucleus	Pterygopalatine ganglion	Secretion of tears
Submandibular and sublingual glands	Superior salivatory nucleus	Submandibular ganglion	Secretion of saliva, vasodilation
Parotid gland	Inferior salivatory nucleus	Otic ganglion	Secretion of saliva, vasodilation
Head, neck (blood vessels, sweat glands, piloerector muscles)	None	None	None
Upper extremity	None	None	None
Heart	Nucleus ambiguus Dorsal motor nucleus of the vagus nerve	Cardiac plexus	Reduced heart rate
Bronchi, lungs	Dorsal motor nucleus of the vagus nerve	Pulmonary plexus	Bronchial constriction and secretion
Stomach	Dorsal motor nucleus of the vagus nerve	Myenteric and submucosal plexus	Peristaltic movement and secretion
Pancreas	Dorsal motor nucleus of the vagus nerve	Pancreatic plexus	Secretion of digestive enzymes
Ascending small intestine, transverse large intestine	Dorsal motor nucleus of the vagus nerve	Ganglia in the myenteric and submucosal plexus	Peristaltic movement and secretion
Descending large intestine, sigmoid, rectum	S3–S4	Ganglia in the myenteric and submucosal plexus	Peristaltic movement and secretion
Adrenal gland	None	None	None
Ureter, bladder	S2–S4	Pelvic plexus	Contraction of bladder wall and inhibition of internal sphincter
Lower extremity	None	None	None

head and thorax are in the lowest cervical segment and the upper and middle thoracic segments, whereas those that control the abdominal and pelvic organs and targets in the lower extremities are in the lower thoracic and upper lumbar segments. The axons that arise from these spinal preganglionic neurons typically extend only a short distance, terminating in a series of paravertebral or sympathetic chain ganglia, which, as the name implies, are arranged in a chain that extends along most of the length of the vertebral column (see Figure 20.1). These preganglionic pathways to the ganglia are known as the white communicating rami because of the relatively light color imparted to the rami by the myelinated axons they contain (see Figure 20.2A). Roughly speaking, these preganglionic spinal neurons are comparable to somatic motor interneurons (see Chapter 15).

The neurons in **sympathetic ganglia** are the primary or lower motor neurons of the sympathetic division in that they directly innervate smooth muscles, cardiac muscle, and glands. The **postganglionic axons** arising from these **paravertebral sympathetic chain** neurons travel to various targets in the body wall, joining the segmental spinal nerves of the corresponding spinal segments by way of the gray communicating rami. These rami are another set of short linking nerves, so named because the unmyelinated postganglionic axons give them a somewhat darker appearance than the myelinated preganglionic linking nerves (see Figure 20.2A).

In addition to innervating the sympathetic chain ganglia, the preganglionic axons that govern the viscera extend a longer distance from the spinal cord in the splanchnic nerves to reach sympathetic ganglia that lie in the chest, abdomen, and pelvis. These **prevertebral ganglia** include sympathetic ganglia in the cardiac plexus, the celiac ganglion, the superior and inferior mesenteric ganglia, and sympathetic ganglia in the pelvic plexus (note that *ganglion* is the singular form, and *ganglia* plural). The postganglionic axons arising from the prevertebral ganglia provide sympathetic innervation to the heart, lungs, gut, kidneys, pancreas, liver, bladder, and reproductive organs (many of these organs also receive some postganglionic innervation from neurons in the sympathetic chain ganglia). Finally, a subset of thoracic preganglionic fibers in the splanchnic nerves innervate the adrenal medulla, which is generally regarded as a sympathetic ganglion modified for a specific endocrine function—namely, the release of catecholamines into the circulation to enhance a widespread sympathetic response to stress. In summary, sympathetic axons contribute to virtually all peripheral nerves, carrying innervation to an enormous range of targets (see Table 20.1).

Cannon's memorable truism that the sympathetic activity prepares the animal for "fight or flight" notwithstanding, the sympathetic division of the visceral motor system is tonically active to maintain sympathetic target function at appropriate levels whatever the circumstances. Nor should the sympathetic system be thought of as responding in an all-or-none fashion; many specific sympathetic reflexes operate more or less independently, as might be expected from the obvious need to specifically control various organ functions (e.g., the heart during exercise, the bladder during urination, and the reproductive organs during sexual intercourse, as described in later sections).

The Parasympathetic Division of the Visceral Motor System

In contrast to the sympathetic division, the preganglionic outflow from the central nervous system to the ganglia of the parasympathetic division stems from neurons whose distribution is limited to the brainstem and the sacral part of the spinal cord (see Figure 20.1). The cranial preganglionic innervation arising from the brainstem, which is analogous to the preganglionic sympathetic outflow from the spinal cord, includes the **Edinger-Westfall nucleus** in the midbrain (which innervates the ciliary ganglion via the oculomotor nerve and mediates the diameter of the pupil in response to light; see Chapter 11), the **superior** and **inferior salivatory nuclei** in the pons and medulla (which innervate the salivary glands and tear glands, mediating salivary secretion and the production of tears), a visceral motor division of the **nucleus ambiguus** in the medulla and the **dorsal motor nucleus of the vagus nerve**, which is also in the medulla. The more dorsal part of the dorsal motor nucleus of the vagus nerve primarily governs glandular secretion via the parasympathetic ganglia located in the viscera of the thorax and abdomen, whereas the more ventral part of the nucleus controls the motor responses of the heart, lungs, and gut elicited by the vagus nerve (e.g., slowing of the heart rate and constricting the bronchioles). Neurons in the ventral-lateral part of the nucleus ambiguus also provide an important source of cardio-inhibitory innervation to the cardiac ganglia via the vagus nerve. In addition, other preganglionic neurons in the nucleus ambiguus innervate parasympathetic ganglia in the submandibular salivary glands and the mediastinum (a different division of the nucleus ambiguus provides branchiomotor innervation of striated muscle in the pharynx and larynx). The location of the parasympathetic brainstem nuclei is shown in Figure 20.3A and B.

The sacral preganglionic innervation arises from neurons in the lateral gray matter of the sacral segments of the spinal cord, which are located in much the same position as the sympathetic preganglionic neurons in the intermediolateral column of the thoracic cord (Figure 20.3C,D). The axons from these neurons travel in the splanchnic nerves to innervate parasympathetic ganglia in the lower third of the colon, rectum, bladder, and reproductive organs.

The **parasympathetic ganglia** innervated by preganglionic outflow from both cranial and sacral levels are in or near the end organs they serve. In this way they differ from the ganglionic targets of the sympathetic system (recall that both the paravertebral chain and prevertebral ganglia are located relatively far from their target organs; see Figure 20.1). An important anatomical difference between sympathetic and parasympathetic ganglia at the cellular level is that sympathetic ganglion cells tend to have extensive dendritic arbors and are, as might be expected from this arrangement, innervated by a large number of preganglionic fibers. Parasympathetic ganglion cells have few if any dendrites and consequently are each innervated by only one or a few preganglionic axons (see Box B in Chapter 22).

The overall function of the parasympathetic system, as Gaskell, Langley, and later Cannon demonstrated, is generally opposite to that of the sympathetic system, serving to increase metabolic and other resources during periods when the animal's circumstances allow it to "rest and digest." In contrast to the sympathetic functions enumerated earlier, the activity of the parasympathetic system constricts the pupils, slows the heart rate, and increases the peristaltic activity of the gut. At the same time, diminished activity in the sympathetic system allows the blood vessels of the skin and gut to dilate, the piloerector muscles to relax, and the outflow of catecholamines from the adrenal medulla to decrease.

Although most organs do (as Gaskell surmised) receive innervation from *both* the sympathetic and parasympathetic divisions of the visceral motor system, some receive only sympathetic innervation. These exceptional targets include the sweat glands, the adrenal medulla, the piloerector muscles of the skin, and most arterial blood vessels (see Table 20.1).

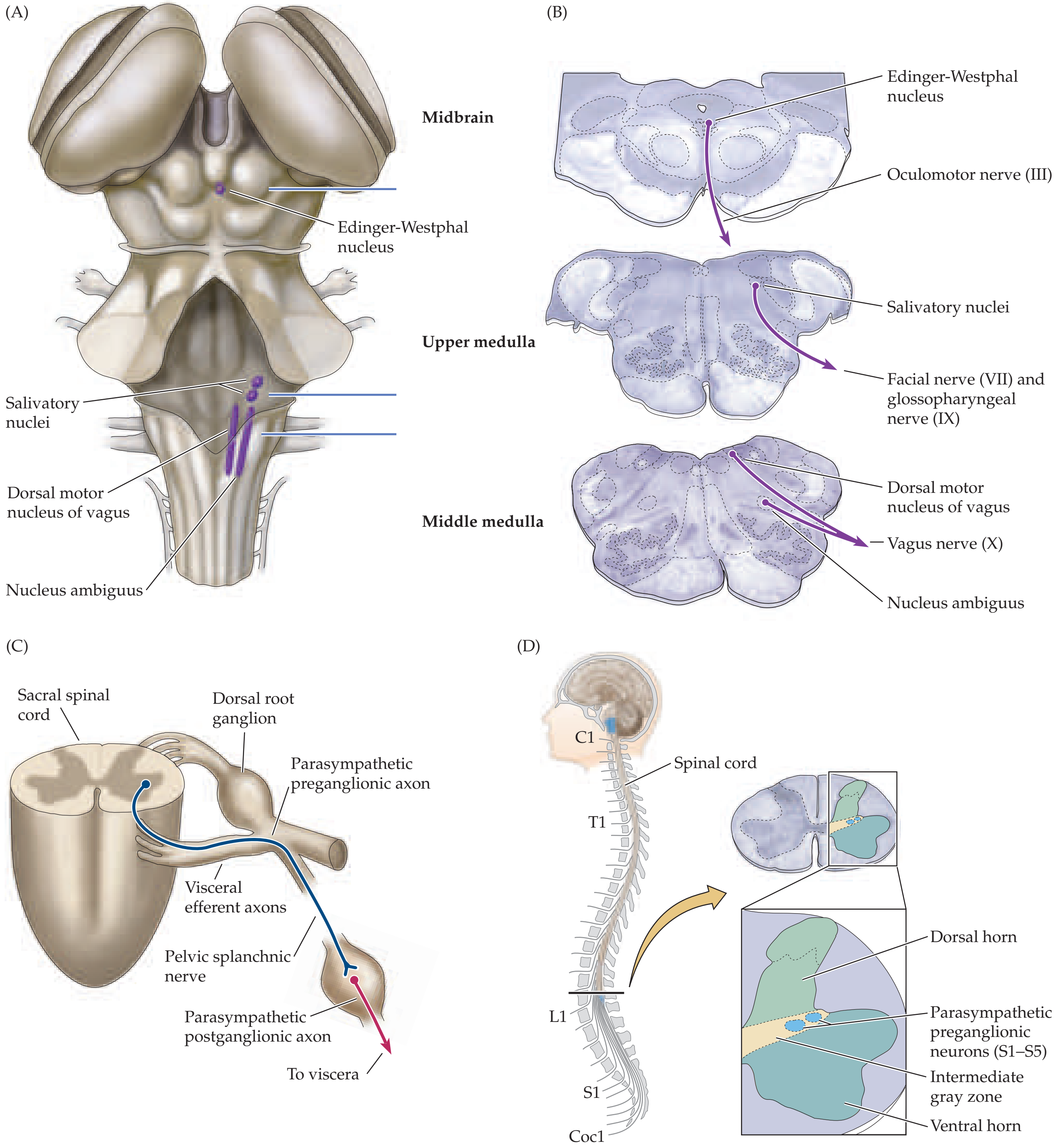

(A)
Midbrain
Edinger-Westphal nucleus
Salivatory nuclei
Dorsal motor nucleus of vagus
Nucleus ambiguus
(B)
Edinger-Westphal nucleus
Oculomotor nerve (III)
Upper medulla
Salivatory nuclei
Facial nerve (VII) and glossopharyngeal nerve (IX)
Middle medulla
Dorsal motor nucleus of vagus
Vagus nerve (X)
Nucleus ambiguus
(C)
Sacral spinal cord
Dorsal root ganglion
Parasympathetic preganglionic axon
Visceral efferent axons
Pelvic splanchnic nerve
Parasympathetic postganglionic axon
To viscera
(D)
C1
Spinal cord
T1
L1
S1
Coc1
Dorsal horn
Parasympathetic preganglionic neurons (S1–S5)
Intermediate gray zone
Ventral horn

Figure 20.3 Organization of the preganglionic outflow to parasympathetic ganglia. (A) Dorsal view of brainstem showing the location of the nuclei of the cranial part of the parasympathetic division of the visceral motor system. (B) Cross section of the brainstem at the relevant levels [indicated by horizontal lines in (A)] showing location of these parasympathetic nuclei. (C) Main features of the parasympathetic preganglionics in the sacral segments of the spinal cord. (D) Cross section of the sacral spinal cord showing location of sacral preganglionic neurons.

The Enteric Nervous System

An enormous number of neurons are specifically associated with the gastrointestinal tract to control its many functions; indeed, more neurons are said to reside in the human gut than in the entire spinal cord. As already noted, the activity of the gut is modulated by both the sympathetic and the parasympathetic divisions of the visceral motor system. However, the gut also has an extensive system of nerve cells in its wall (as do its accessory organs such as the pancreas and gallbladder) that do not fit neatly into the sympathetic or parasympathetic divisions of the visceral motor system (Figure 20.4A). To a surprising degree, these neurons and the complex enteric

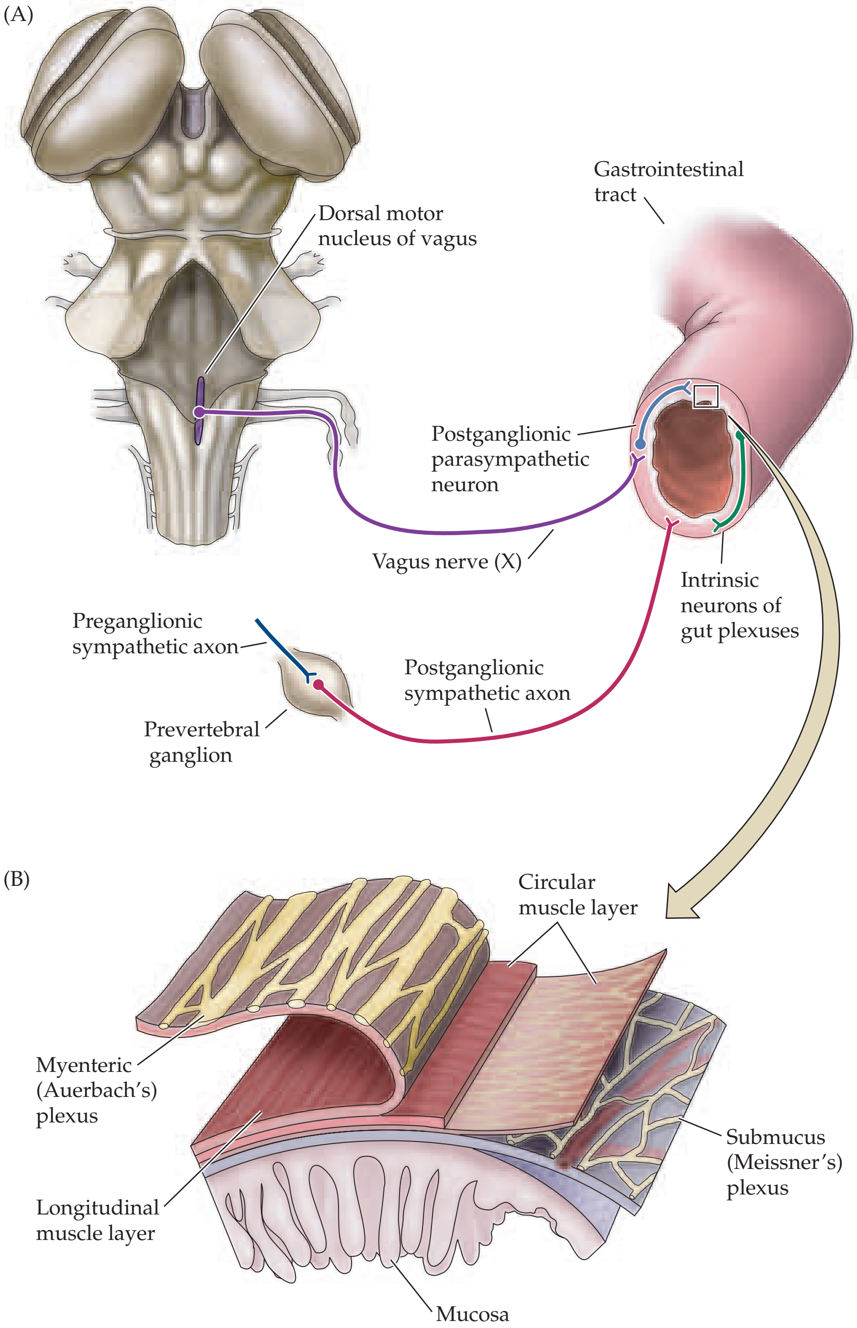

(A)
Gastrointestinal tract
Dorsal motor nucleus of vagus
Postganglionic parasympathetic neuron
Vagus nerve (X)
Intrinsic neurons of gut plexuses
Preganglionic sympathetic axon
Postganglionic sympathetic axon
Prevertebral ganglion
(B)
Circular muscle layer
Myenteric (Auerbach's) plexus
Submucus (Meissner's) plexus
Longitudinal muscle layer
Mucosa

Figure 20.4 Organization of the enteric component of the visceral motor system. (A) Sympathetic and parasympathetic innervation of the enteric nervous system, and the intrinsic neurons of the gut. (B) Detailed organization of nerve cell plexuses in the gut wall. The neurons of the submucus plexus (Meissner's plexus) are concerned with the secretory aspects of gut function, and the myenteric plexus (Auerbach's plexus) with the motor aspects of gut function (e.g., peristalsis).

plexuses in which they are found operate more or less independently according to their own reflex rules; as a result, many gut functions continue perfectly well without sympathetic or parasympathetic supervision (peristalsis, for example, occurs in isolated gut segments *in vitro*). Thus, most investigators prefer to classify the enteric nervous system as a separate component of the visceral motor system.

The neurons in the gut wall include local and centrally projecting sensory neurons that monitor mechanical and chemical conditions in the gut, local circuit neurons that integrate this information, and motor neurons that influence the activity of the smooth muscles in the wall of the gut and glandular secretions (e.g., of digestive enzymes, mucus, stomach acid, and bile). This complex arrangement of nerve cells intrinsic to the gut is organized into (1) the myenteric (or Auerbach's) plexus, which is specifically concerned with regulating the musculature of the gut; and (2) the submucus (or Meissner's) plexus, which is located, as the name implies, just beneath the mucus membranes of the gut and is concerned with chemical monitoring and glandular secretion (Figure 20.4B).

As already mentioned, the preganglionic parasympathetic neurons that influence the gut are primarily in the dorsal motor nucleus of vagus nerve in the brainstem and the intermediate gray zone in the sacral spinal cord segments. The preganglionic sympathetic innervation that modulates the action of the gut plexuses derives from the thoraco-lumbar cord, primarily by way of the celiac, superior, and inferior mesenteric ganglia.

Sensory Components of the Visceral Motor System

Although the focus of this unit is "movement and its central control," it is also important to understand the sources of visceral sensory information and the means by which this input becomes intergrated in the central nervous system. Generally speaking, afferent activity arising from the viscera serves two important functions: (1) it provides feedback input to local reflexes that modulate moment-to-moment visceral motor activity within individual organs; and (2) it serves to inform higher integrative centers of more complex patterns of stimulation that may signal potentially threatening conditions and/or require the coordination of more widespread visceral motor, somatic motor, neuroendocrine, and behavioral activities (Figure 20.5). The **nucleus of the solitary tract** in the medulla is the central structure in the brain that receives visceral sensory information and distributes it accordingly to serve both purposes.

The afferent fibers that provide this visceral sensory input arise from cell bodies that lie in the dorsal root ganglia (as is the case of somatic sensory modalities; see Chapters 8 and 9) and the sensory ganglia associated with the glossopharyngeal and vagus cranial nerves. However, there are far fewer visceral sensory neurons (by a factor of about 10) in comparison to mechanosensory neurons that innervate the skin and deeper somatic structures. This relative sparseness of peripheral visceral sensory innervation accounts in part for why most visceral sensations are diffuse and difficult to localize precisely.

The spinal visceral sensory neurons in the dorsal root ganglia send axons peripherally, through symapthetic nerves, ending in sensory receptor specializations such as nerve endings that are sensitive to pressure or stretch (in the walls of the heart, bladder, and gastrointestinal tract); endings that innervate specialized chemosensitive cells (oxygen-sensitive cells in the carotid bodies); or nociceptive endings that respond to damaging stretch, ischemia,

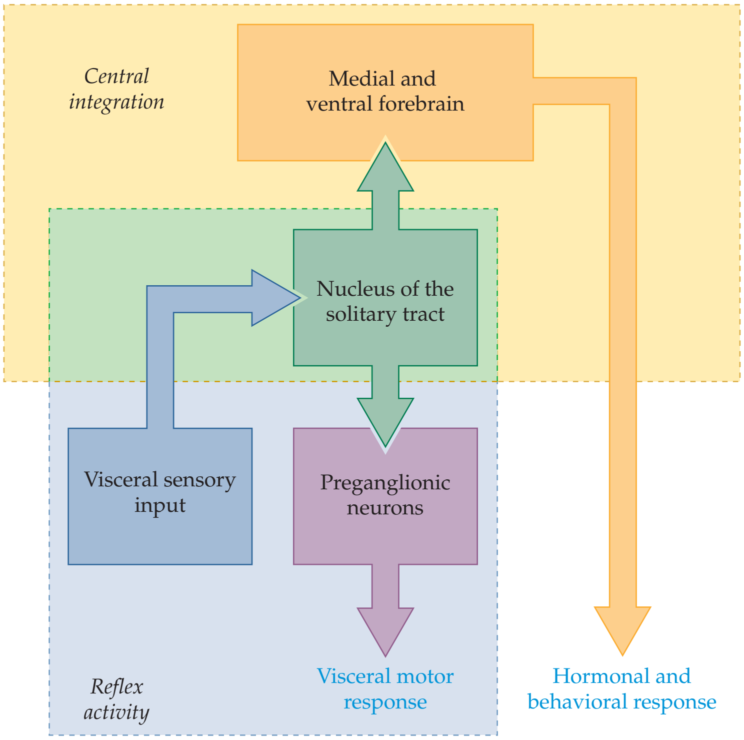


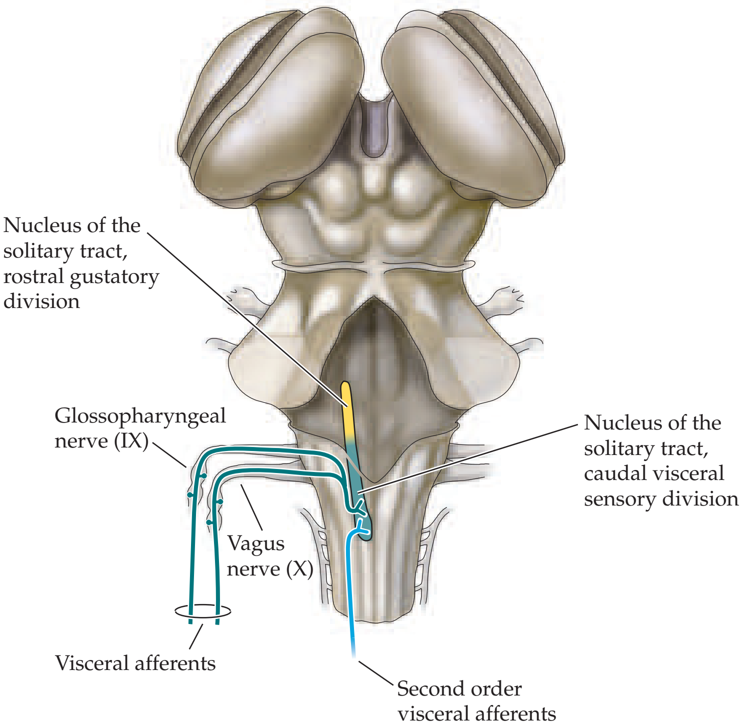
Figure 20.5 Distribution of visceral sensory information by the nucleus of the solitary tract to serve either local reflex responses or more complex hormonal and behavioral responses via integration within a central autonomic network. As illustrated in Figure 20.7, forebrain centers also provide input to visceral motor effector systems in the brainstem and spinal cord.

or the presence of irritating chemicals. The central axonal processes of these dorsal root ganglion neurons terminate on second-order neurons and local interneurons in the dorsal horn and on intermediate gray regions of the spinal cord. Some primary visceral sensory axons terminate near the lateral horn, where the preganglionic neurons of sympathetic and parasympathetic divisions are located; these terminals mediate visceral reflex activity in a manner not unlike the segmental somatic motor reflexes described in Chapter 15.

In the dorsal horn, many of the second-order neurons that receive visceral sensory inputs are actually neurons of the anterolateral system, which also receive nociceptive and/or crude mechanosensory input from more superficial sources (see Chapter 9). As described in Box A of Chapter 9, this is one means by which painful visceral sensations may be “referred” to more superficial somatic territories. Axons of these second-order visceral sensory neurons travel rostrally in the ventrolateral white matter of the spinal cord and the lateral sector of the brainstem and eventually reach the ventral posterior complex of the thalamus. However, the axons of other second-order visceral sensory neurons terminate before reaching the thalamus; the principal target of these axons is the nucleus of the solitary tract (Figure 20.6). Other brainstem targets of second-order visceral sensory axons are visceral motor centers in the medullary **reticular formation** (see Box A in Chapter 16).

In the last decade, it has become clear that visceral sensory information, especially axons related to painful visceral sensations, also ascends the central nervous system by another spinal pathway. Second-order neurons whose cell bodies are located near the central canal of the spinal cord send their axons through the dorsal columns to terminate in the dorsal column

Figure 20.6 Organization of sensory input to the visceral motor system. Afferent input from the cranial nerves relevant to visceral sensation (as well as afferent input ascending from the spinal cord not shown here) converge on the caudal division of the nucleus of the solitary tract (the rostral division is a gustatory relay; see Chapter 14).


Nucleus of the solitary tract, rostral gustatory division
Glossopharyngeal nerve (IX)
Nucleus of the solitary tract, caudal visceral sensory division
Vagus nerve (X)
Visceral afferents
Second order visceral afferents

nuclei, where third-order neurons relay visceral nociceptive signals to the ventral posterior thalamus. Although the existence of this visceral pain pathway in the dorsal columns complicates the simplistic view of the dorsal column–medial lemniscal pathway as a discriminitive mechanosensory projection and the anterolateral system as a pain pathway, mounting empirical and clinical evidence highlights the importance of this newly discovered dorsal column pain pathway in the central transmission of visceral nociception (see Box B in Chapter 9).

In addition to these spinal visceral afferents, general visceral sensory inputs from thoracic and upper abdominal organs, as well as from viscera in the head and neck, enter the brainstem directly via the glossopharyngeal and vagus cranial nerves (see Figure 20.6). These glossopharyngeal and vagal visceral afferents also terminate in the nucleus of the solitary tract. This nucleus, as described in the next section, integrates a wide range of visceral sensory information and transmits this information directly (and indirectly) to relevant visceral motor nuclei, the brainstem reticular formation, as well as several key regions in the medial and ventral forebrain that coordinate visceral motor activity (see Figure 20.5).

Finally, unlike the somatic sensory system (where virtually all sensory signals gain access to conscious neural processing), sensory fibers related to the viscera convey only limited information to consciousness. For example, most of us are completely unaware of the subtle changes in peripheral vascular resistance that raise or lower our mean arterial blood pressure, yet such covert visceral afferent information is essential for the functioning of autonomic reflexes and the maintenance of homeostasis. Typically, it is only painful visceral sensations and signals that are integrated into emotional experience and expression (see Chapter 28) that enter conscious awareness.

Central Control of Visceral Motor Functions

The nucleus of the solitary tract—and in particular, the caudal part of this nucleus—is a key integrative center for reflexive control of visceral motor function and an important relay of visceral sensory information to other brainstem nuclei and forebrain structures (Figure 20.7; see also Figure 20.5). The rostral part of this nucleus, as described in Chapter 14, is a gustatory relay receiving input from primary taste afferents (cranial nerves VII, IX, and X) and sending projections to the gustatory nucleus in the ventral-posterior thalamus. The caudal visceral sensory part of the nucleus of the solitary tract provides input to primary visceral motor nuclei, such as the dorsal motor nucleus of the vagus nerve and the nucleus ambiguus. It also projects to "premotor" autonomic centers in the medullary reticular formation, and to

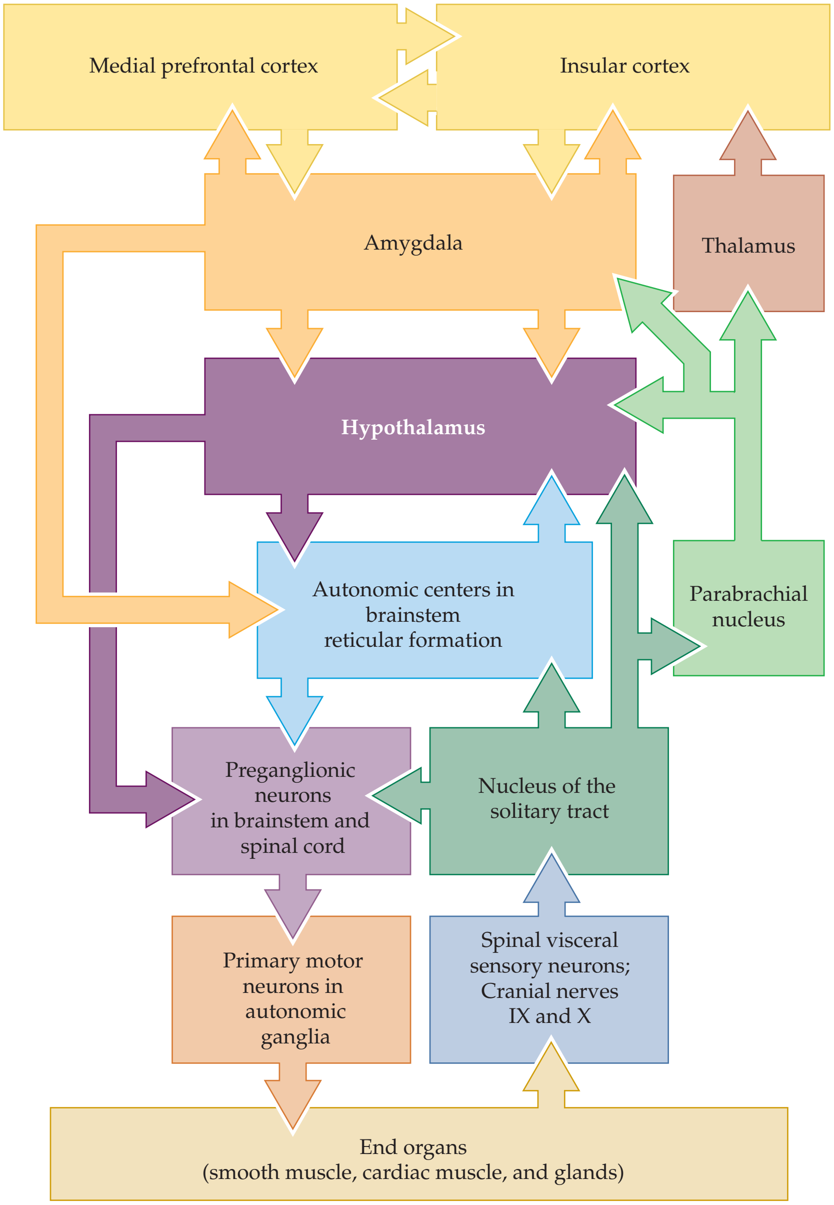

Medial prefrontal cortex
Insular cortex
Amygdala
Thalamus
Hypothalamus
Autonomic centers in brainstem reticular formation
Parabrachial nucleus
Preganglionic neurons in brainstem and spinal cord
Nucleus of the solitary tract
Primary motor neurons in autonomic ganglia
Spinal visceral sensory neurons; Cranial nerves IX and X
End organs (smooth muscle, cardiac muscle, and glands)

Figure 20.7 A central autonomic network for the control of visceral motor function. Overview of connections within the central autonomic network. The distribution of visceral sensory information within this network is illustrated on the right side of the figure and the generation of visceral motor commands is shown on the left. However, extensive interconnections among autonomic centers in the forebrain (between the amygdala and associated cortical regions or hypothalamus, for example) militate against a strict parsing of this network into afferent and efferent limbs. The hypothalamus is a key structure in this network that integrates visceral sensory input and higher order visceral motor signals (see Box A).

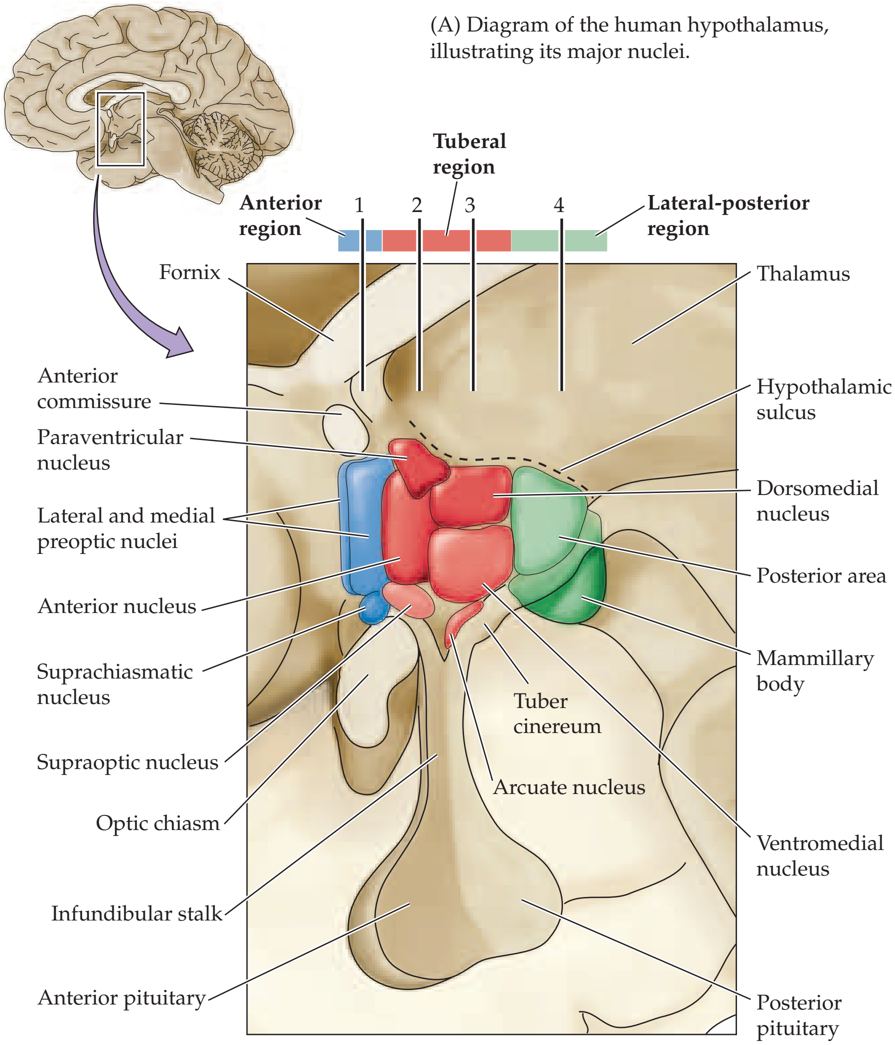
Box A

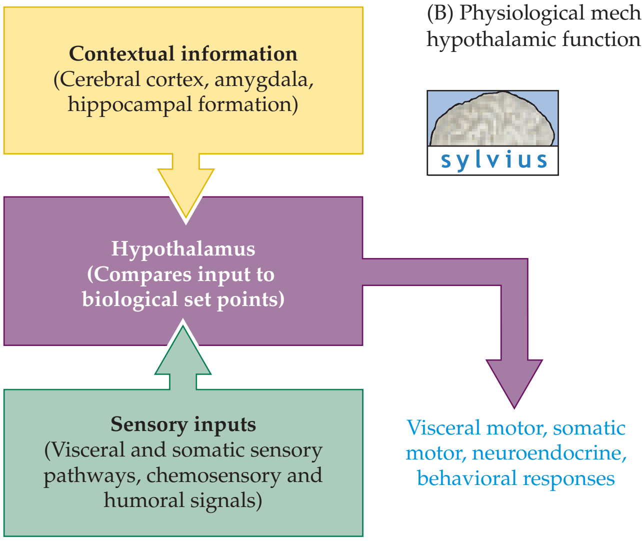
The Hypothalamus

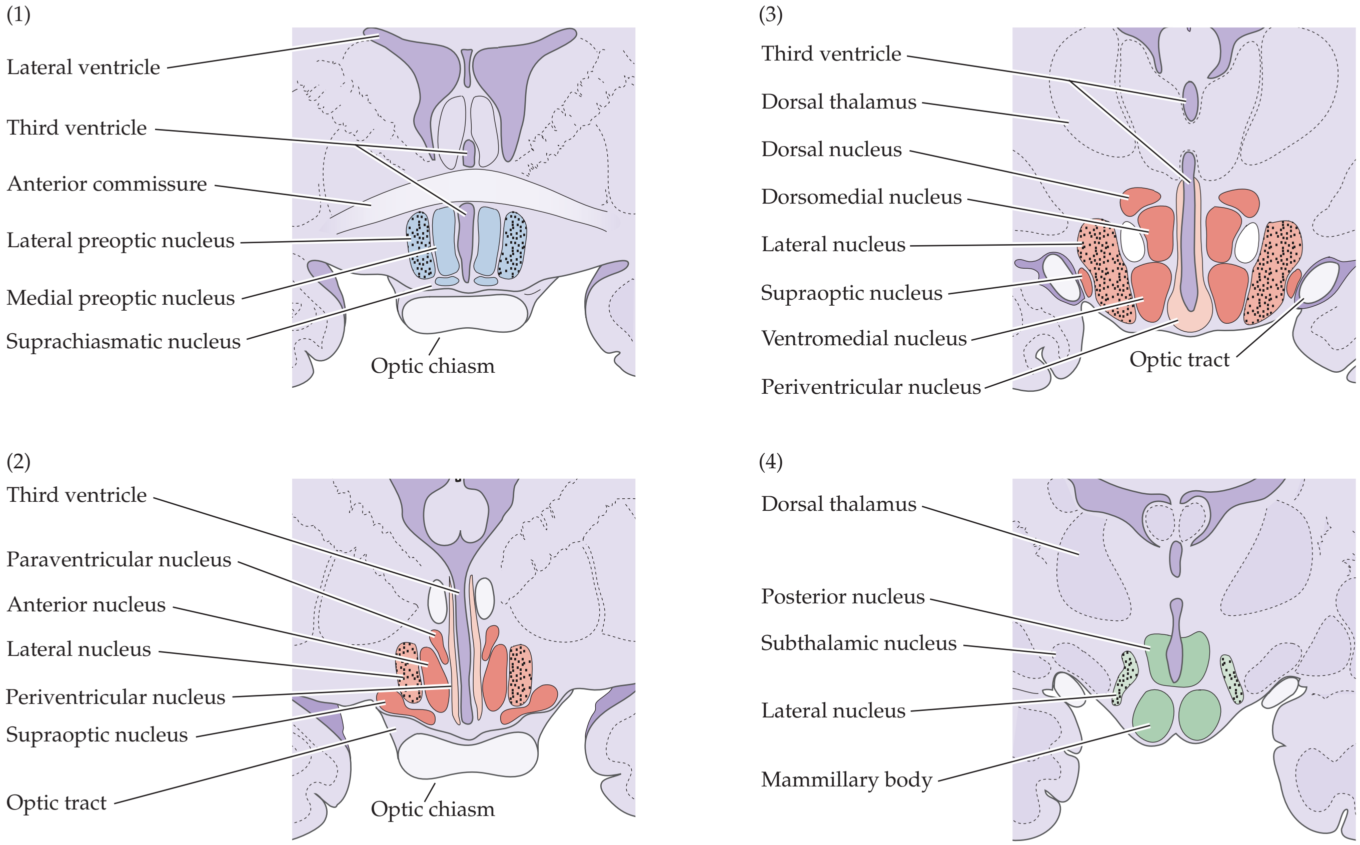
The hypothalamus is located at the base of the forebrain, bounded by the optic chiasm rostrally and the midbrain tegmentum caudally. It forms the floor and ventral walls of the third ventricle and is continuous through the infundibular stalk with the posterior pituitary gland, as illustrated in Figure A. Given its central position in the brain and its proximity to the pituitary, it is not surprising that the hypothalamus integrates information from the forebrain, brainstem, spinal cord, and various intrinsic chemosensitive neurons.

What is surprising about this structure is the remarkable diversity of homeostatic functions that are governed by this relatively small region of the forebrain. The diverse functions in which hypothalamic involvement is at least partially understood include: *the control of blood flow* (by promoting adjustments in cardiac output, vasomotor tone, blood osmolarity, and renal clearance, and by motivating drinking and salt consumption); the *regulation of energy metabolism* (by monitoring blood glucose levels and regulating feeding behavior, digestive functions, metabolic rate, and temperature); the *regulation of reproductive activity* (by influencing gender identity, sexual orientation and mating behavior and, in females, by governing menstrual cycles, pregnancy, and lactation); and the *coordination of responses to threatening conditions* (by governing the release of stress hormones, modulating the balance between sympathetic and parasympathetic tone, and influencing the regional distribution of blood flow).

Despite the impressive scope of hypothalamic control, the individual components of the hypothalamus utilize similar physiological mechanisms to exert their influence over these many functions (Figure B). Thus, hypothalamic circuits receive sensory and contextual information, compare that information with biological set


(A) Diagram of the human hypothalamus, illustrating its major nuclei.
Tuberal region
Anterior region
1
2
3
4
Lateral-posterior region
Fornix
Thalamus
Anterior commissure
Hypothalamic sulcus
Paraventricular nucleus
Dorsomedial nucleus
Lateral and medial preoptic nuclei
Posterior area
Anterior nucleus
Suprachiasmatic nucleus
Mammillary body
Tuber cinereum
Supraoptic nucleus
Arcuate nucleus
Optic chiasm
Ventromedial nucleus
Infundibular stalk
Anterior pituitary
Posterior pituitary


(B) Physiological mechanisms underlying hypothalamic function.
Contextual information (Cerebral cortex, amygdala, hippocampal formation)
Hypothalamus (Compares input to biological set points)
Sensory inputs (Visceral and somatic sensory pathways, chemosensory and humoral signals)
Visceral motor, somatic motor, neuroendocrine, behavioral responses


(1)
Lateral ventricle
Third ventricle
Anterior commissure
Lateral preoptic nucleus
Medial preoptic nucleus
Suprachiasmatic nucleus
Optic chiasm
(2)
Third ventricle
Paraventricular nucleus
Anterior nucleus
Lateral nucleus
Periventricular nucleus
Supraoptic nucleus
Optic tract
Optic chiasm
(3)
Third ventricle
Dorsal thalamus
Dorsal nucleus
Dorsomedial nucleus
Lateral nucleus
Supraoptic nucleus
Ventromedial nucleus
Periventricular nucleus
Optic tract
(4)
Dorsal thalamus
Posterior nucleus
Subthalamic nucleus
Lateral nucleus
Mammillary body

(C) Coronal sections through the human hypothalamus (see Figure A for location of sections 1–4). Color coding of the nuclei illustrates the two dimensions by which hypothalamic nuclei are subdivided (see text). Blue, red, and green illustrate nuclei in the anterior, tuberal, and posterior regions, respectively. The relative shading of these hues illustrates the three mediolateral zones: Lighter shading represents nuclei in the periventricular zone, whereas darker shades represent medial zone nuclei. Nuclei in the lateral zone are stippled. (1) Section through the anterior region illustrating the preoptic and suprachiasmatic nuclei. (2) Rostral tuberal region. (3) Caudal tuberal region. (4) Section through the posterior region illustrating the mammillary bodies.

points, and activate relevant visceral motor, neuroendocrine, and somatic motor effector systems that restore homeostasis and/or elicit appropriate behavioral responses.

Like the overlying thalamus—and consistent with the scope of hypothalamic functions—the hypothalamus comprises a large number of distinct nuclei, each with its own specific pattern of connections and functions. The nuclei, most of which are intricately interconnected, can be grouped in three longitudinal regions referred to as *periventricular*, *medial*, and *lateral*. They can also be grouped along the anterior–posterior dimension, the groups being those nuclei in the *anterior* (or preoptic), *tuberal*, and *posterior* regions (Figure C). The anterior-pariventricular group contains the suprachiasmatic nucleus, which receives direct retinal input and drives circadian rhythms (see Chapter 27). More scattered neurons in the periventricular region (located along the wall of the third ventricle) manufacture peptides known as releasing or inhibiting factors that control the secretion of a variety of hormones by the anterior pituitary. The axons of these neurons project to the median eminence, a region at the junction of the hypothalamus and pituitary stalk, where the peptides are secreted into the portal circulation that supplies the anterior pituitary.

The medial-tuberal region nuclei ("tuberal" refers to the *tuber cinereum*, the anatomical name given to the middle portion of the inferior surface of the hypothalamus) include the paraventricular and supraoptic nuclei, which contain the neurosecretory neurons whose axons extend into the posterior pituitary. With appropriate stimulation, these neurons secrete oxytocin or vasopressin (antidiuretic hormone) directly into the bloodstream. Other neurons in the paraventricular nucleus project to autonomic centers in the reticular formation, as well as preganglionic neurons of the sympathetic and parasympathetic divisions in the

Continued on next page

Box A

The Hypothalamus (*continued*)

brainstem and spinal cord; these cells are thought to exert hypothalamic control over the visceral motor system. The paraventricular nucleus receives inputs from other hypothalamic zones, which are in turn related to the cerebral cortex, hippocampus, amygdala, and other central structures that are all capable of influencing visceral motor function.

Also in the region of the hypothalamus are the dorsomedial and ventromedial nuclei, which are involved in feeding, reproductive and parenting behavior, thermoregulation, and water balance. These nuclei receive inputs from structures of the limbic system, as well as from visceral sensory nuclei in the brainstem (e.g., the nucleus of the solitary tract).

Finally, the lateral region of the hypothalamus is really a rostral continuation of the midbrain reticular formation (see Box A in Chapter 16). Thus, the neurons of the lateral region are not grouped into nuclei, but are scattered among the fibers of the medial forebrain bundle, which runs through the lateral hypothalamus. These cells control behavioral arousal and shifts of attention, especially as related to reproductive activities.

In summary, the hypothalamus regulates an enormous range of physiological and behavioral activities and serves as the key controlling center for visceral motor activity and for homeostatic functions generally.

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higher integrative centers in the amygdala (specifically, the central group of amygdaloid nuclei; see Box B in Chapter 28) and hypothalamus (see Box A and below). In addition, the nucleus of the solitary tract projects to the **parabrachial nucleus** (so named because it envelopes the superior cerebellar peduncle, which is also known by its Latin name, the *brachium conjunctivum*). The parabrachial nucleus, in turn, provides additional visceral sensory relays to the hypothalamus, amygdala, thalamus, and medial prefrontal and insular cortex (see Figure 20.7; for clarity, the cortical projections of the parabrachial nucleus are omitted).

Although one might propose that the posterior insular cortex serves as the primary visceral sensory area and the medial prefrontal cortex as the primary visceral motor area, it is more useful to emphasize the interactions among these cortical areas and related subcortical structures; taken together, they constitute a **central autonomic network**. This network accounts for the integration of visceral sensory information with input from other sensory modalities and higher cognitive centers that process semantic and emotional experiences. Involuntary visceral reactions such as blushing in response to consciously embarrassing stimuli, vasoconstriction and pallor in response to fear, and autonomic responses to sexual situations are examples of the integrated activity of this network. Indeed, autonomic function is intimately related to emotional processing, as emphasized in Chapter 28.

A key component of this central autonomic network that deserves special consideration is the **hypothalamus**. This heterogeneous collection of nuclei in the base of the diencephalon serves as the major center for the coordination and expression of visceral motor activity (Box A). The major outflow from the relevant hypothalamic nuclei is directed toward "autonomic centers" in the reticular formation; these centers can be thought of as dedicated premotor circuits that coordinate the efferent activity of preganglionic visceral motor neurons. They organize specific visceral functions such as cardiac reflexes,

reflexes that control the bladder, reflexes related to sexual function, and other critical autonomic reflexes underlying respiration and vomiting (see Box A in Chapter 16).

In addition to these important connections to the reticular formation, hypothalamic control of visceral motor function is also exerted more directly by projections to the cranial nerve nuclei that contain parasympathetic preganglionic neurons, and to the sympathetic and parasympathetic preganglionic neurons in the spinal cord. Nevertheless, the autonomic centers of the reticular formation and the preganglionic visceral motor neurons that they control are competent to function autonomously should disease or injury impede the governance of the hypothalamus over the many bodily systems that maintain homeostasis. The general organization of this central autonomic control is summarized in Figure 20.7; some important clinical manifestations of damage to this descending system are illustrated in Box B; Box C shows the relevance of this central control to one prevalent category of human disorder (obesity).

Neurotransmission in the Visceral Motor System

The neurotransmitter functions of the visceral motor system are of enormous importance in clinical practice, and drugs that act on the autonomic system are among the most important in the clinical armamentarium. Moreover, autonomic transmitters have played a major role in the history of efforts to understand synaptic function. Consequently, neurotransmission in the visceral motor system deserves special comment (see also Chapter 6).

Acetylcholine is the primary neurotransmitter of both sympathetic and parasympathetic preganglionic neurons. Nicotinic receptors on autonomic ganglion cells are ligand-gated ion channels that mediate a so-called fast EPSP (much like nicotinic receptors at the neuromuscular junction). In contrast, muscarinic acetylcholine receptors on ganglion cells are members of the 7-transmembrane G-protein-linked receptor family, and they mediate slower synaptic responses (see Chapters 6 and 7).The primary action of muscarinic receptors in autonomic ganglion cells is to close K^+ channels, making the neurons more excitable and generating a prolonged EPSP. Acting in concert with the muscarinic activities are neuropeptides that serve as co-neurotransmitters at the ganglionic synapses. As described in Chapter 6, peptide neurotransmitters also tend to exert slowly developing and long-lasting effects on postsynaptic neurons. As a result of these two acetylcholine receptor types and a rich repertoire of neuropeptide transmitters, ganglionic synapses mediate both rapid excitation and a slower modulation of autonomic ganglion cell activity.

The postganglionic effects of autonomic ganglion cells on their smooth muscle, cardiac muscle, or glandular targets are mediated by two primary neurotransmitters: norepinephrine (NE) and acetylcholine (ACh). For the most part, sympathetic ganglion cells release norepinephrine onto their targets (a notable exception is the cholinergic sympathetic innervation of sweat glands), whereas parasympathetic ganglion cells typically release acetylcholine. As expected from the foregoing account, these two neurotransmitters usually have opposing effects on their target tissue—contraction versus relaxation of smooth muscle, for example.

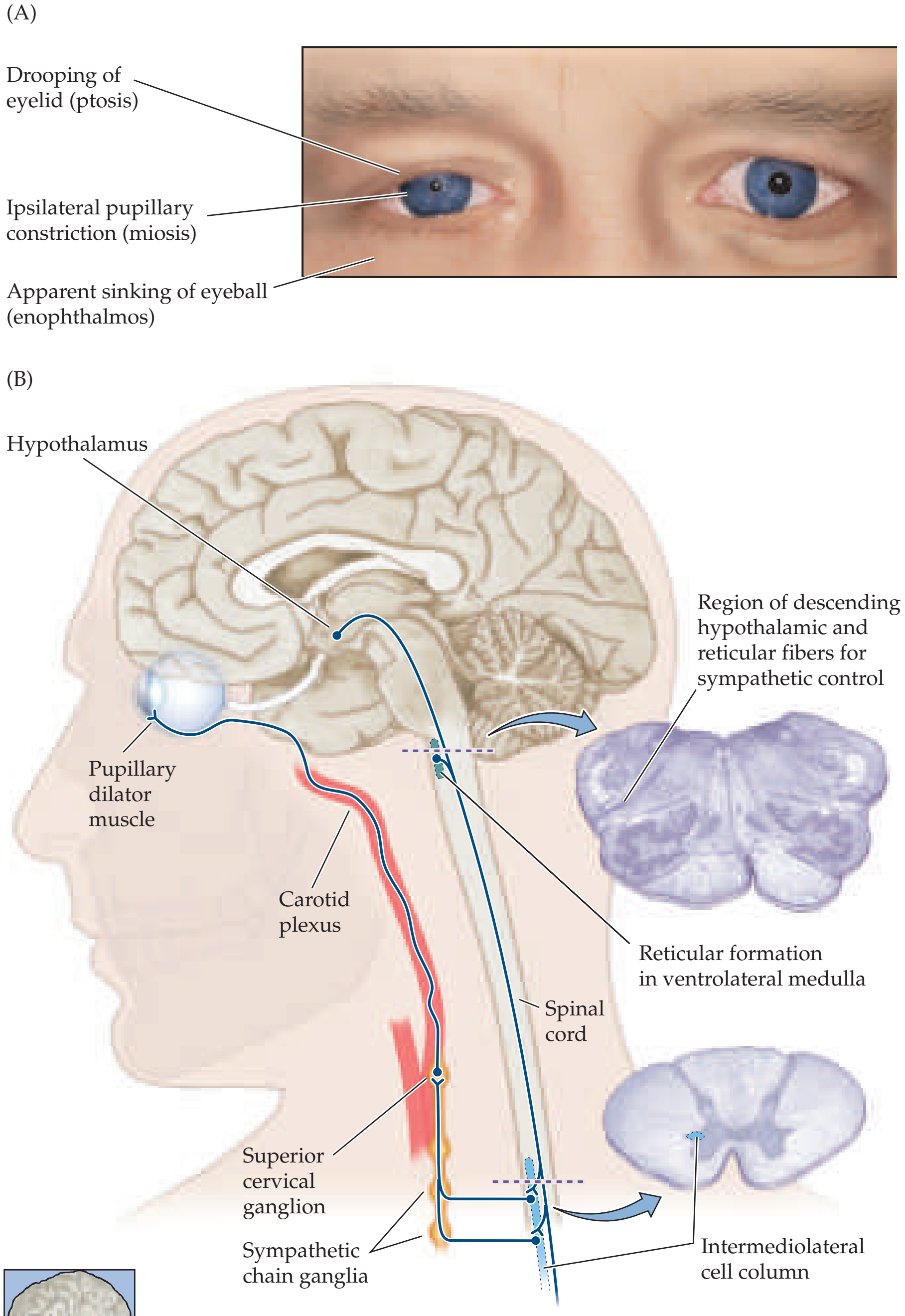
As described in Chapters 6 and 7, the specific effects of either ACh or NE are determined by the type of receptor expressed in the target tissue, and the downstream signaling pathways to which these receptors are linked. Peripheral sympathetic targets generally have two subclasses of noradrenergic

Box B

Horner's Syndrome

The characteristic clinical presentation of damage to the pathway that controls the sympathetic division of the visceral motor system to the head and neck is called Horner's syndrome, after the Swiss ophthalmologist who first described this clinical picture in the mid-nineteenth century. The main features, as illustrated in Figure A, are decreased diameter of the pupil on the side of the lesion (miosis), a droopy eyelid (ptosis), and a sunken appearance of the affected eye (enophthalmos). Less obvious signs are decreased sweating, increased skin temperature, and flushing of the skin on the same side of the face and neck.

All these signs are explained by a loss of sympathetic tone due to damage somewhere along the pathway that connects visceral motor centers in the hypothalamus and reticular formation with sympathetic preganglionic neurons in the intermediolateral cell column of the thoracic spinal cord (Figure B). Lesions that interrupt these fibers often spare the descending parasympathetic pathways, which are located more medially in the brainstem and are more diffuse. The sympathetic preganglionic targets that are affected by such lesions include the neurons in the intermediolateral column in spinal segments T1–T3 that control the dilator muscle of the iris and the tone in smooth muscles of the eyelid and globe, the paralysis of which leads to miosis, ptosis, and enophthalmos. The flushing and decreased sweating are likewise the result of diminished sympathetic tone, in this case governed by intermediolateral column neurons in somewhat lower thoracic segments (~T3–T8). Damage to the descending sympathetic pathway in the brainstem will, of course, affect sweating and vascular tone in the rest of the body on the side of the lesion. However, if the damage is to the upper thoracic outflow (as is more typical), the upper thoracic chain, or the superior cervical ganglion, then the manifestations of Horner's syndrome will be limited to the head and neck. Typical causes in these sites are stab or gunshot wounds or other traumatic injuries to the head and neck, and tumors of the apex of the lung, thyroid, or cervical lymph nodes.


(A)
Drooping of eyelid (ptosis)
Ipsilateral pupillary constriction (miosis)
Apparent sinking of eyeball (enophthalmos)
(B)
Hypothalamus
Region of descending hypothalamic and reticular fibers for sympathetic control
Pupillary dilator muscle
Carotid plexus
Reticular formation in ventrolateral medulla
Spinal cord
Superior cervical ganglion
Sympathetic chain ganglia
Intermediolateral cell column

sylvius

(A) Major features of the clinical presentation of Horner's syndrome. (B) Diagram of the descending sympathetic pathways arising in the hypothalamus and reticular formation that can be interrupted to cause Horner's syndrome. Damage to the preganglionic neurons in the upper thoracic cord, to the superior cervical ganglion, or to the cervical sympathetic trunk can also cause Horner's syndrome (see also Figure 20.1). The transverse lines indicate the level of the sections shown at right.

TABLE 20.2
Summary of Adrenergic Receptor Types and Some of Their Effects in Sympathetic Targets

Receptor	*Tissue*	*Response*
α_1	Smooth muscle of blood vessels, iris, ureter, hairs, uterus, bladder	Contraction of smooth muscle
	Smooth muscle of gut	Relaxation of smooth muscle
	Heart muscle	Positive inotropic effect ($\beta_1 >> \alpha_1$)
	Salivary gland	Secretion
	Adipose tissue	Glycogenolysis, gluconeogenesis
	Sweat glands	Secretion
	Kidney	Na^+ reabsorbed
α_2	Adipose tissue	Inhibition of lipolysis
	Pancreas	Inhibition of insulin release
	Smooth muscle of blood vessels	Contraction
β_1	Heart muscle	Positive inotropic effect; positive chronotropic effect
	Adipose tissue	Lipolysis
	Kidney	Renin release
β_2	Liver	Glycogenolysis, gluconeogenesis
	Skeletal muscle	Glycogenolysis, lactate release
	Smooth muscle of bronchi, uterus, gut, blood vessels	Relaxation
	Pancreas	Insulin secretion
	Salivary glands	Thickened secretions

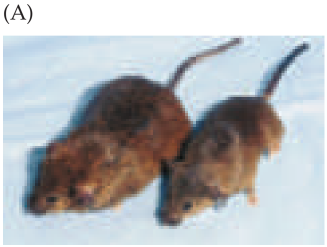
receptors in their cell membranes, referred to as α and β receptors. Like muscarinic ACh receptors, both α and β receptors and their subtypes belong to the 7-transmembrane G-protein-coupled class of cell surface receptors. The different distribution of these receptors in sympathetic targets allows for a variety of postsynaptic effects mediated by norepinephrine released from postganglionic sympathetic nerve endings (Table 20.2).

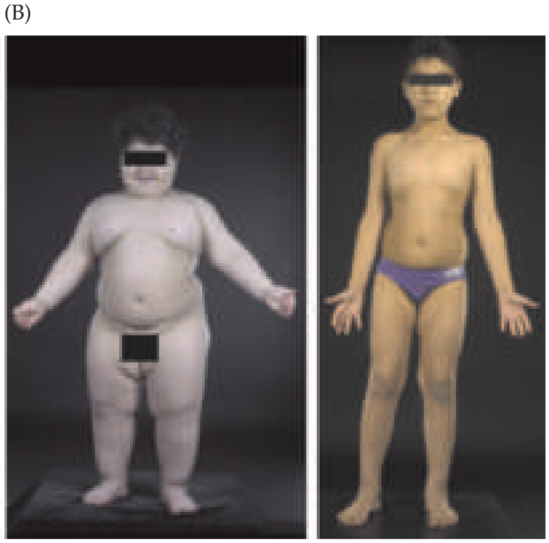
The effects of acetylcholine released by parasympathetic ganglion cells onto smooth muscles, cardiac muscle, and glandular cells also vary according to the subtypes of muscarinic cholinergic receptors found in the peripheral target (Table 20.3). The two major subtypes are known as M1 and M2 receptors, M1 receptors being found primarily in the gut and M2 receptors in the cardiovascular system. (Another subclass of muscarinic receptors, M3, occurs in both smooth muscle and glandular tissues.) Muscarinic receptors are coupled to a variety of intracellular signal transduction mechanisms that modify K^+ and Ca^{2+} channel conductances. They can also activate nitric oxide synthase, which promotes the local release of NO in some parasympathetic target tissues (see, for example, the section below on autonomic control of sexual function).

In contrast to the relatively restricted responses generated by norepinephrine and acetylcholine released by sympathetic and parasympathetic ganglion cells, respectively, neurons of the enteric nervous system achieve an enormous diversity of target effects by virtue of many different neurotrans-

Box C

Obesity and the Brain





(A) A *POMC* knockout mouse (left) and a wild-type littermate (right). (B) The effect of leptin treatment in a human. At age 3 years, the subject weighed 42 kg (left); at age 7 years, following treatment, the same child weighed 32 kg (right). (A from Yaswen et al., 1999, B from O'Rahilly et al., 2003.)

Obesity and its relationship to a broad range of diseases—including diabetes, cardiovascular disease and cancer—has become a major public health concern in most developed countries, particularly the United States. Whereas the signature of obesity is obviously an excess of body fat, the underlying cause or causes are generally thought to lie in abnormal regulation by the brain circuits that control appetite and satiety. This fact makes weight loss particularly difficult for many obese individuals. Thus, understanding of the central nervous systems mechanisms that regulate food intake and metabolism are essential for developing effective strategies to combat this very serious health problem.

The brain regulates appetite and satiety (the feeling of fullness following a meal) via the neural activity that is modulated by chemical signals that are secreted into the circulation by fat storing adipose tissues throughout the body. Since this feedback loop entails some of the central components of the visceral motor system, in addition to endocrine mechanisms via insulin and growth hormone, it is discussed here. The peptide **ghrelin** is secreted by the stomach prior to feeding, presumably as a signal of hunger; adipocytes (the cells that concentrate lipid in fatty tissues) secrete **leptin** into the circulation following feeding, presumably as a signal for satiety. The receptors for these peptides are concentrated in small groups of neurons in the ventrolateral and anterior hypothalamus (see Box A), which contact additional hypothalamic neurons in the arcuate region. These grehlin- and leptin-responsive cells modulate the activity of neurons expressing the opiomelanocortin propeptide (POMC) and the subsequent secretion of α-melanocyte secreting hormone (α-MSH), one of the peptides encoded by the POMC transcript. This hormone evidently regulates appetite and satiety by acting on specific receptors (particularly the melanocortin receptor subtype called MCR-4) located on additional populations of hypothalamic and brainstem neurons (particularly those in the nucleus of the solitary tract), as well as by endocrine mechanisms that remain poorly understood.

The interactions of leptin, grehlin, α-MSH and MCR-4 were first determined in animal models. Two recessive mutations in mice—the obese (*ob*/*ob*) and the misnamed diabetic (*db*/*db*) mice—were identified based on excessive body weight and failure to regulate food intake. When each mutation was cloned, the mutant gene in *ob* mice turned out to be the gene for leptin, and the *db* gene that for the leptin receptor. Mutations in the *POMC* (Figure A) and *MCR4* genes also lead to obesity in mice. The results of inactivation of the *ghrelin* gene are less clear; however, pharmacological and physiological studies associate changes in ghrelin levels with altered feeding and weight loss. Studies in mice have thus provided a solid framework for examining the physiological mechanisms regulating food intake in humans. Nonetheless, their relevance to morbid human obesity remained unclear until recently.

Genetic analysis of individuals in human pedigrees with extreme obesity (measured body mass indices and weight/height ratios) revealed mutations in one or more of the leptin, leptin receptor, or *MCR4* genes. As a result, these individuals have little sense of satiety after eating, and thus fail to regulate food intake based on signals other than gastric distension and pain. How this pathophysiology is related to less extreme degrees of obesity is not yet known, but is being intensely studied because of its implications for normal weight control.

The emerging understanding of body weight regulation by hypothalamic circuits that are modulated by feedback from by hormonal signals from fat tissues has provided new ways of thinking about pharmacological therapies for weight control. While leptin mimetics have proven generally ineffective, leptin administration in human subjects with leptin deficiencies does reduce food intake and obesity (Figure B). Currently, there is great interest in drugs that modulate α-MSH signaling via MCR-4. Although no effective pharmacological therapies presently exist, there is hope that such drugs, when combined with behavioral changes in dietary practices, will effectively combat this often intractable and increasingly common health problem.

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Saper, C. B., T. C. Chou and J. K. Elmquist (2002) The need to feed: Homeostatic and hedonic control of eating. Neuron 36: 199–21.

TABLE 20.3
Summary of Cholinergic Receptor Types and Some of Their Effects in Parasympathetic Targets

Receptor	*Tissue*	*Response*
Nicotinic	Most parasympathetic targets (and all autonomic ganglion cells)	Relatively fast postsynaptic response
Muscarinic (M1)	Smooth muscles and glands of the gut	Smooth muscle contraction and glandular secretion (relatively slow response)
Muscarinic (M2)	Smooth and cardiac muscle of cardiovascular system	Smooth muscle contraction; some inotropic effect on cardiac muscle
Muscarinic (M3)	Smooth muscles and glands of all targets	Smooth muscle contraction, glandular secretion

mitters, most of which are neuropeptides associated with specific cell groups in either the myenteric or submucous plexuses mentioned earlier. The details of these agents and their actions are beyond the scope of this introductory account.

Visceral Motor Reflex Functions

Many examples of specific autonomic functions could be used to illustrate in more detail how the visceral motor system operates. The three outlined here—control of cardiovascular function, control of the bladder, and control of sexual function—have been chosen primarily because of their importance in human physiology and clinical practice.

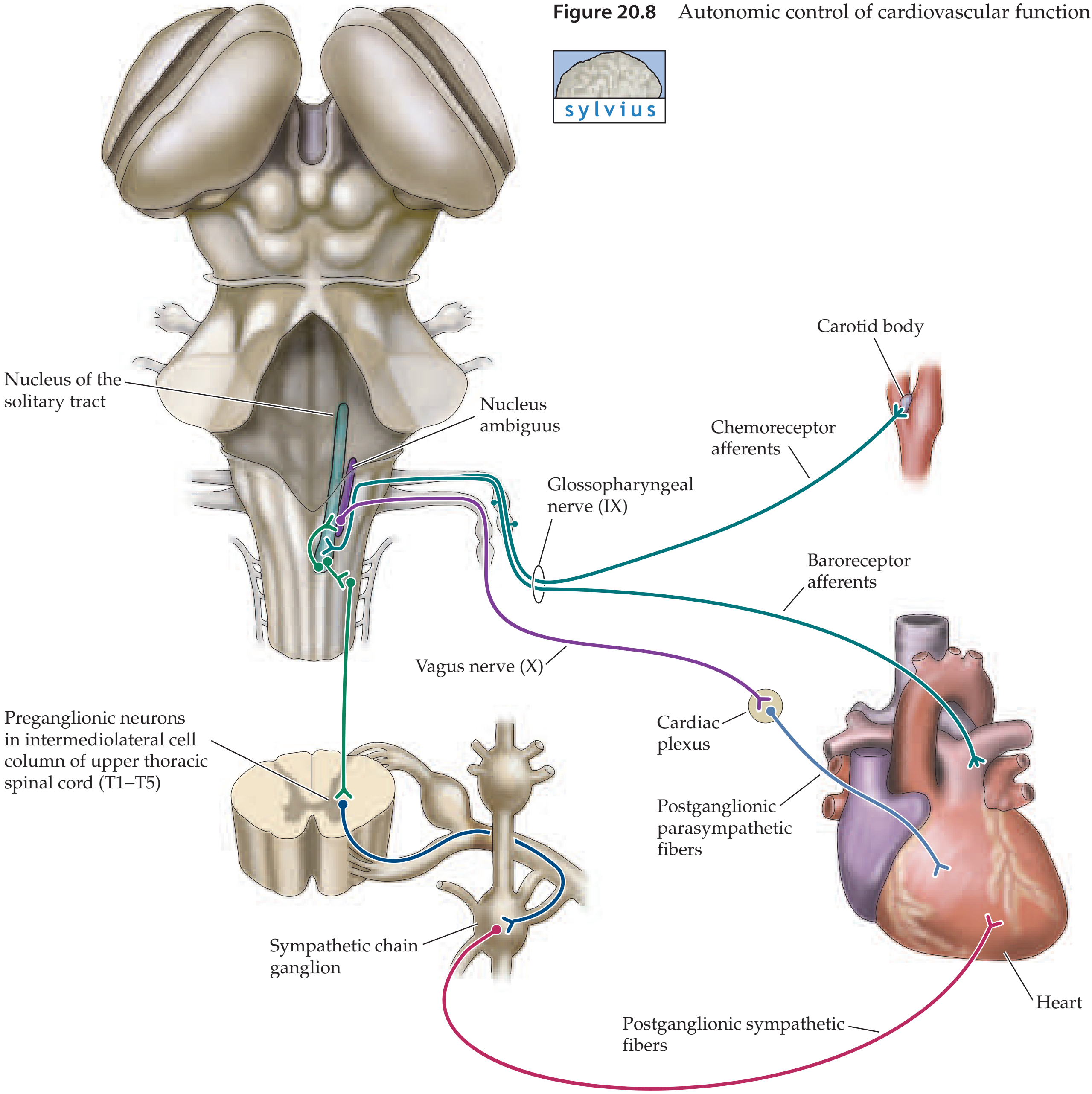
Autonomic Regulation of Cardiovascular Function

The cardiovascular system is subject to precise reflex regulation so that an appropriate supply of oxygenated blood can be reliably provided to different body tissues under a wide range of circumstances. The sensory monitoring for this critical homeostatic process entails primarily mechanical (barosensory) information about pressure in the arterial system and, secondarily, chemical (chemosensory) information about the levels of oxygen and carbon dioxide in the blood. The parasympathetic and sympathetic activity relevant to cardiovascular control is determined by the information supplied by these sensors.

The mechanoreceptors (called baroreceptors) are located in the heart and major blood vessels; the chemoreceptors are located primarily in the carotid bodies, which are small, highly specialized organs located at the bifurcation of the common carotid arteries (some chemosensory tissue is also found in the aorta). The nerve endings in baroreceptors are activated by deformation as the elastic elements of the vessel walls expand and contract. The chemoreceptors in the carotid bodies and aorta respond directly to the partial pressure of oxygen and carbon dioxide in the blood. Both afferent systems convey their status via the vagus nerve to the nucleus of the solitary tract (Figure 20.8), which relays this information to the hypothalamus and the relevant autonomic centers in the reticular formation.

The afferent information derived from changes in arterial pressure and blood gas levels reflexively modulates the activity of the relevant visceral

Figure 20.8 Autonomic control of cardiovascular function.


Carotid body
Nucleus of the solitary tract
Nucleus ambiguus
Chemoreceptor afferents
Glossopharyngeal nerve (IX)
Baroreceptor afferents
Vagus nerve (X)
Preganglionic neurons in intermediolateral cell column of upper thoracic spinal cord (T1–T5)
Cardiac plexus
Postganglionic parasympathetic fibers
Sympathetic chain ganglion
Heart
Postganglionic sympathetic fibers

motor pathways and, ultimately, of target smooth and cardiac muscles and other more specialized structures. For example, a rise in blood pressure activates baroreceptors that, via the pathway illustrated in Figure 20.8, inhibit the tonic activity of sympathetic preganglionic neurons in the spinal cord. In parallel, the pressure increase stimulates the activity of the parasympathetic preganglionic neurons in the nucleus ambiguus and the dorsal motor nucleus of the vagus that influence heart rate. The carotid chemoreceptors also have some influence, but this is a less important drive than that stemming from the baroreceptors.

As a result of this shift in the balance of sympathetic and parasympathetic activity, the stimulatory noradrenergic effects of postganglionic sympathetic innervation on the cardiac pacemaker and cardiac musculature is reduced (these effects are abetted by the decreased output of catecholamines from the adrenal medulla and the decreased vasoconstrictive effects of sympathetic innervation on the peripheral blood vessels). At the same time, activation of the cholinergic parasympathetic innervation of the heart decreases the discharge rate of the cardiac pacemaker in the sinoatrial node and slows the ventricular conduction system. These parasympathetic influences are mediated by an extensive series of parasympathetic ganglia in and near the heart, which release acetylcholine onto cardiac pacemaker cells and cardiac muscle fibers. As a result of this combination of sympathetic and parasympathetic effects, heart rate and the effectiveness of atrial and ventricular mycoardial contraction are reduced and the peripheral arterioles dilate, thus lowering the blood pressure.

In contrast to this sequence of events in response to raised blood pressure, a fall in blood pressure (as might occur from blood loss) has the opposite effect—it inhibits parasympathetic activity while increasing sympathetic activity. As a result, norepinephrine is released from sympathetic postganglionic terminals, increasing the rate of cardiac pacemaker activity and enhancing cardiac contractility, at the same time increasing release of catecholamines from the adrenal medulla (which further augments these and many other sympathetic effects that enhance the response to this threatening situation). Norepinephrine released from the terminals of sympathetic ganglion cells also acts on the smooth muscles of the arterioles to increase the tone of the peripheral vessels, particularly those in the skin, subcutaneous tissues, and muscles, thus shunting blood away from these tissues to those organs where oxygen and metabolites are urgently needed to maintain function (e.g., brain, heart, and kidneys in the case of blood loss). If these reflex sympathetic responses fail to raise the blood pressure sufficiently (in which case the patient is said to be in shock), the vital functions of these organs begin to fail, often catastrophically.

A more mundane circumstance that requires a reflex autonomic response to a fall in blood pressure is standing up. Rising quickly from a prone position produces a shift of some 300–800 milliliters of blood from the thorax and abdomen to the legs, resulting in a sharp (approximately 40%) decrease in the output of the heart. The adjustment to this normally occurring drop in blood pressure (called *orthostatic hypotension*) must be rapid and effective, as evidenced by the dizziness sometimes experienced in this situation. Indeed, normal individuals can briefly lose consciousness as a result of blood pooling in the lower extremities, which is the usual cause of fainting among healthy individuals who stand still for abnormally long periods.

The sympathetic innervation of the heart arises from the preganglionic neurons in the intermediolateral column of the spinal cord, extending from roughly the first through fifth thoracic segments (see Table 20.1). The primary visceral motor neurons are in the adjacent thoracic paravertebral and prevertebral ganglia of the cardiac plexus. The parasympathetic preganglionics, as already mentioned, are in the nucleus ambiguus and the dorsal motor nucleus of the vagus nerve, projecting to parasympathetic ganglia in and around the heart and great vessels.

Autonomic Regulation of the Bladder

The autonomic regulation of the bladder provides a good example of the interplay between components of the somatic motor system that are subject to volitional control (we obviously have voluntary control over urination), and the sympathetic and parasympathetic divisions of the visceral motor system, which operate involuntarily.

The arrangement of afferent and efferent innervation of the bladder is shown in Figure 20.9. The parasympathetic control of the bladder musculature, the contraction of which causes bladder emptying, originates with neurons in the sacral spinal cord segments (S2–S4) that innervate visceral motor neurons in parasympathetic ganglia in or near the bladder wall. Mechanoreceptors in the bladder wall supply visceral afferent information to the spinal cord and to higher autonomic centers in the brainstem (primarily the nucleus of the solitary tract), which in turn project to the various central

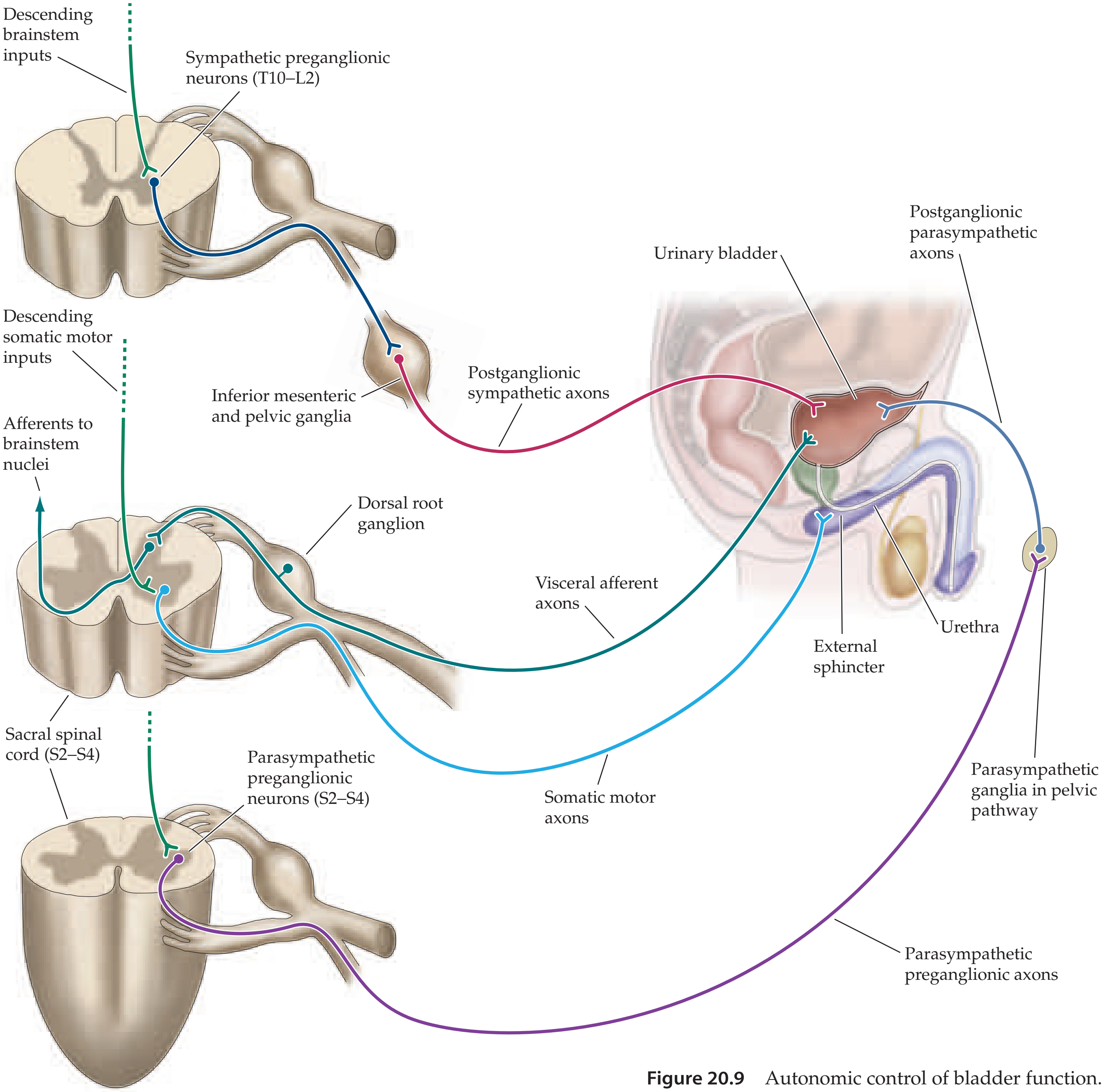

Descending brainstem inputs
Sympathetic preganglionic neurons (T10–L2)
Postganglionic parasympathetic axons
Urinary bladder
Descending somatic motor inputs
Postganglionic sympathetic axons
Inferior mesenteric and pelvic ganglia
Afferents to brainstem nuclei
Dorsal root ganglion
Visceral afferent axons
External sphincter
Urethra
Sacral spinal cord (S2–S4)
Parasympathetic preganglionic neurons (S2–S4)
Somatic motor axons
Parasympathetic ganglia in pelvic pathway
Parasympathetic preganglionic axons

Figure 20.9 Autonomic control of bladder function.

coordinating centers for bladder function in the pontine reticular formation and anterior-medial hypothalamus.

The sympathetic innervation of the bladder originates in the lower thoracic and upper lumbar spinal cord segments (T10–L2), the preganglionic axons running to sympathetic neurons in the inferior mesenteric ganglion and the ganglia of the pelvic plexus. The postganglionic fibers from these ganglia travel in the hypogastric and pelvic nerves to the bladder, where sympathetic activity causes the internal urethral sphincter to close (postganglionic sympathetic fibers also innervate the blood vessels of the bladder, and in males the smooth muscle fibers of the prostate gland). Stimulation of this pathway in response to a modest increase in bladder pressure from the accumulation of urine thus closes the internal sphincter and inhibits the contraction of the bladder wall musculature, allowing the bladder to fill. At the same time, moderate distension of the bladder inhibits parasympathetic activity (which would otherwise contract the bladder and allow the internal sphincter to open). When the bladder is full, afferent activity conveying this information centrally increases parasympathetic tone and decreases sympathetic activity, causing the internal sphincter muscle to relax and the bladder to contract. In this circumstance, the urine is held in check by the voluntary somatic motor innervation of the external urethral sphincter muscle (see Figure 20.9).

The voluntary control of the external sphincter is mediated by α-motor neurons of the ventral horn in the sacral spinal cord segments (S2–S4), which cause the striated muscle fibers of the sphincter to contract. During bladder filling (and subsequently, until circumstances permit urination) these neurons are active, keeping the external sphincter closed and preventing bladder emptying. During urination (or *voiding*, as clinicians often call this process), this tonic activity is temporarily inhibited, leading to relaxation in the external sphincter muscle. Thus, urination results from the coordinated activity of sacral parasympathetic neurons and temporary inactivity of the α-motor neurons of the voluntary motor system.

The central governance of these events stems from the reticular formation of the rostral pons, the relevant pontine circuitry being referred to as the micturition center (*micturition* is also “medicalese” for urination). As many as five other central regions have been implicated in the coordination of urinary functions, including the locus coeruleus, the anterior-medial hypothalamus, the septal nuclei, and several cortical regions. The cortical regions primarily concerned with the voluntary control of bladder function include the paracentral lobule, the cingulate gyrus, and the prefrontal cortex. This functional distribution accords with the motor representation of perineal musculature in the medial part of the primary motor cortex (see Chapter 16), and the planning functions of the frontal lobes (see Chapter 25), which are equally pertinent to bodily functions (remembering to stop by the bathroom before going on a long trip, for instance).

Importantly, paraplegic patients, or patients who have otherwise lost descending control of the sacral spinal cord, continue to exhibit autonomic regulation of bladder function, since urination is eventually stimulated reflexively at the level of the sacral cord by sufficient bladder distension. Unfortunately, this reflex is not fully efficient in the absence of descending motor control, resulting in a variety of problems in paraplegics and others with diminished or absent central control of bladder function. The major difficulty is incomplete bladder emptying, which often leads to chronic urinary tract infections from the culture medium provided by retained urine, and thus the need for an indwelling catheter to ensure adequate drainage.

Autonomic Regulation of Sexual Function

Much like control of the bladder, sexual responses are mediated by the coordinated activity of sympathetic, parasympathetic, and somatic innervation. Although these reflexes differ in detail in males and females, basic similarities allow the two sexes to be considered together, not only in humans but in mammals generally. The relevant autonomic effects include: (1) the mediation of vascular dilation, which causes penile or clitoral erection; (2) stimulation of prostatic or vaginal secretions; (3) smooth muscle contraction of the vas deferens during ejaculation in males or rhythmic vaginal contractions during orgasm in females; and (4) contractions of the somatic pelvic muscles that accompany orgasm in both sexes.

Like the urinary tract, the reproductive organs receive preganglionic parasympathetic innervation from the sacral spinal cord, preganglionic sympathetic innervation from the outflow of the lower thoracic and upper lumbar spinal cord segments, and somatic motor innervation from α-motor neurons in the ventral horn of the lower spinal cord segments (Figure 20.10). The sacral parasympathetic pathway controlling the sexual organs in both males and females originates in the sacral segments S2–S4 and reaches the target organs via the pelvic nerves. Activity of the postganglionic neurons in the relevant parasympathetic ganglia causes dilation of penile or clitoral arteries, and a corresponding relaxation of the smooth muscles of the venous (cavernous) sinusoids, which leads to expansion of the sinusoidal spaces. As a result, the amount of blood in the tissue is increased, leading to a sharp rise in the pressure and an expansion of the cavernous spaces (i.e., erection). The mediator of the smooth muscle relaxation leading to erection is not acetylcholine (as in most postganglionic parasympathetic actions), but nitric oxide (see Chapter 7). The drug sildenafil (Viagra®), for instance, acts by stimulating the activity of guanylate cyclase, which increases the conversion of GTP to cyclic GMP, mimicking the action of NO on the cGMP pathway, thus enhancing the relaxation of the venous sinusoids and promoting erection in males with erectile dysfunction. Parasympathetic activity also provides excitatory input to the vas deferens, seminal vesicles, and prostate in males, or vaginal glands in females.

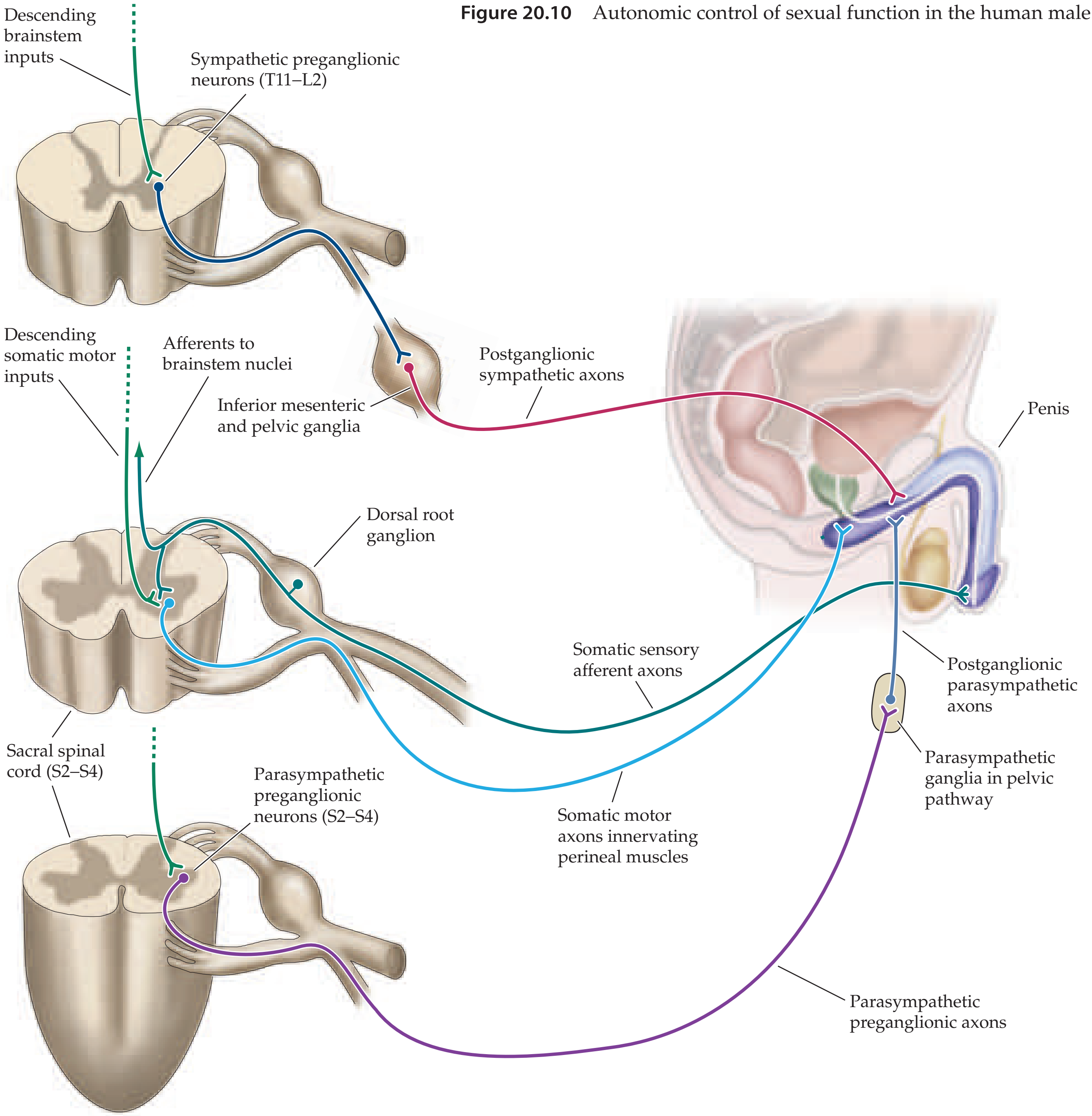
In contrast, sympathetic activity causes vasoconstriction and loss of erection. The lumbar sympathetic pathway to the sexual organs originates in the thoraco-lumbar segments (T1–L2) and reaches the target organs via the corresponding sympathetic chain ganglia and the inferior mesenteric and pelvic ganglia, as in the case of the autonomic bladder control.

The afferent effects of genital stimulation are conveyed centrally from somatic sensory endings via the dorsal roots of S2–S4, eventually reaching the somatic sensory cortex (reflex sexual excitation may also occur by local stimulation, as is evident in paraplegics). The reflex effects of such stimulation are increased parasympathetic activity, which, as noted, causes relaxation of the smooth muscles in the wall of the sinusoids and subsequent erection.

Finally, the somatic component of reflex sexual function arises from α-motor neurons in the lumbar and sacral spinal cord segments. These neurons provide excitatory innervation to the bulbocavernosus and ischiocavernosus muscles, which are active during ejaculation in males and mediate the contractions of the perineal (pelvic floor) muscles that accompany orgasm in both male and females.

Sexual functions are governed centrally by the anterior-medial and medial-tuberal zones of the hypothalamus, which contain a variety of nuclei pertinent to visceral motor control and reproductive behavior (see Box A).

Figure 20.10 Autonomic control of sexual function in the human male.


Descending brainstem inputs
Sympathetic preganglionic neurons (T11–L2)
Descending somatic motor inputs
Afferents to brainstem nuclei
Inferior mesenteric and pelvic ganglia
Postganglionic sympathetic axons
Penis
Dorsal root ganglion
Somatic sensory afferent axons
Postganglionic parasympathetic axons
Parasympathetic ganglia in pelvic pathway
Sacral spinal cord (S2–S4)
Parasympathetic preganglionic neurons (S2–S4)
Somatic motor axons innervating perineal muscles
Parasympathetic preganglionic axons

Although they remain poorly understood, these nuclei act as integrative centers for sexual responses and are also thought to be involved in more complex aspects of sexuality, such as sexual preference and gender identity (see Chapter 29). The relevant hypothalamic nuclei receive inputs from several areas of the brain, including—as one might imagine—the cortical and subcortical structures concerned with emotion, hedonic reward, and memory (see Chapters 28 and 30).

Summary

Sympathetic and parasympathetic ganglia, which contain the primary visceral motor neurons that innervate smooth muscles, cardiac muscle, and glands, are controlled by preganglionic neurons in the spinal cord and brainstem. The sympathetic preganglionic neurons that govern ganglion cells in the sympathetic division of the visceral motor system arise from neurons in the thoracic and upper lumbar segments of the spinal cord; parasympathetic preganglionic neurons, in contrast, are located in the brainstem and sacral spinal cord. Sympathetic ganglion cells are distributed in the sympathetic chain (paravertebral) and prevertebral ganglia, whereas the parasympathetic motor neurons are more widely distributed in ganglia that lie within or near the organs they control. Most autonomic targets receive inputs from both the sympathetic and parasympathetic systems, which act in a generally antagonistic fashion. The diversity of autonomic functions is achieved primarily by different types of receptors for the two primary classes of postganglionic autonomic neurotransmitters, norepinephrine in the case of the sympathetic division and acetylcholine in the parasympathetic division. The visceral motor system is regulated by sensory feedback provided by dorsal root and cranial nerve sensory ganglion cells that make local reflex connections in the spinal cord or brainstem and project to the nucleus of the solitary tract in the brainstem, and by descending pathways from the hypothalamus and brainstem reticular formation, the major controlling centers of the visceral motor system (and of homeostasis more generally). The importance of the visceral motor control of organs such as the heart, bladder, and reproductive organs—and the many pharmacological means of modulating autonomic function—have made visceral motor control a central theme in clinical medicine.

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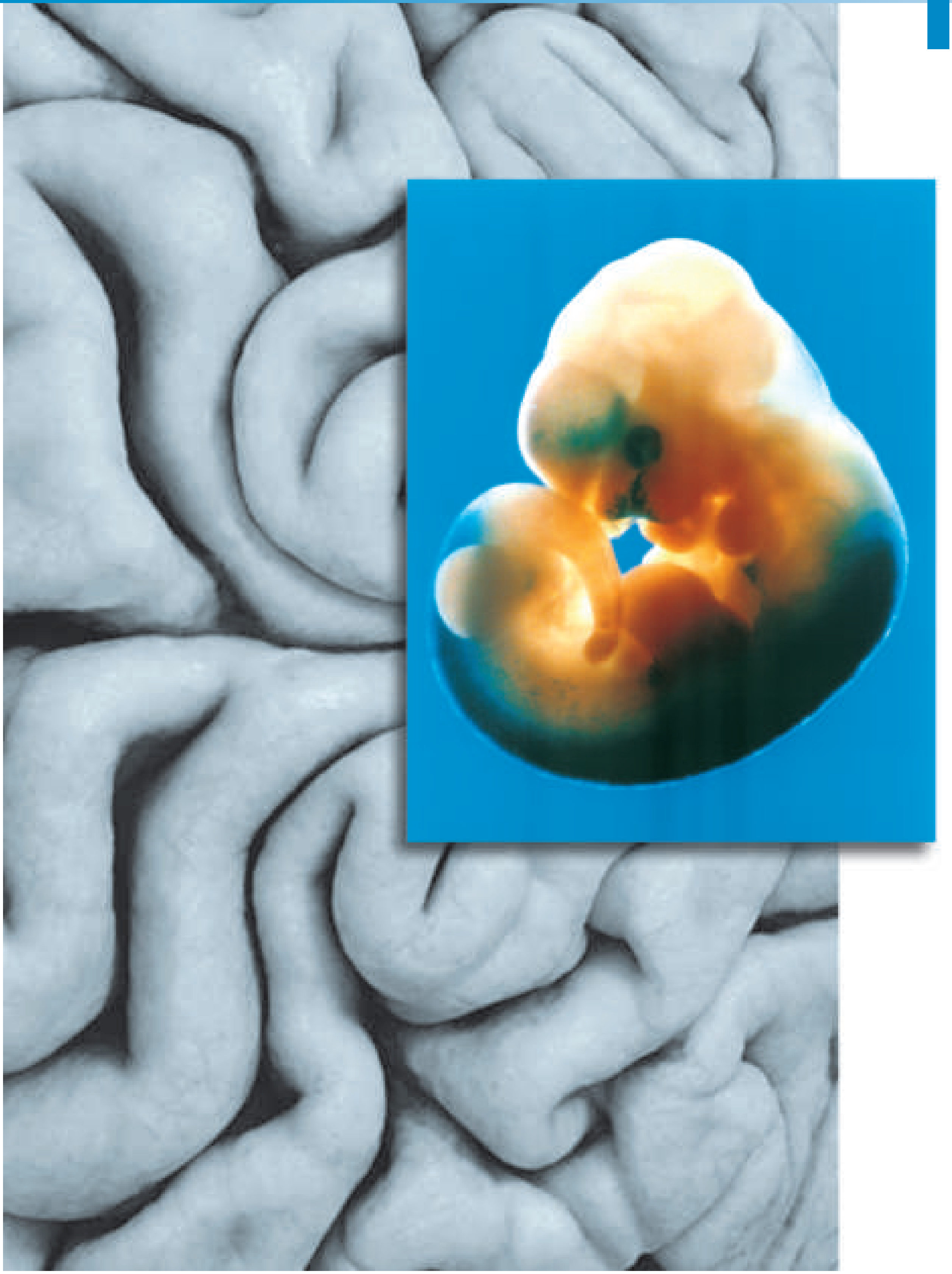
The Changing Brain

IV



UNIT IV

THE CHANGING BRAIN

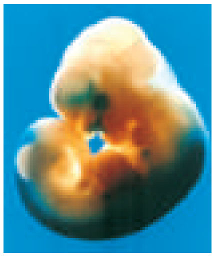
21 *Early Brain Development*
22 *Construction of Neural Circuits*
23 *Modification of Brain Circuits as a Result of Experience*
24 *Plasticity of Mature Synapses and Circuits*

A mammalian embryo in which cells in the developing nervous system responding to the signaling molecule retinoic acid have been labeled by means of a reporter gene. (Courtesy of Anthony-Samuel LaMantia and Elwoood Linney.)

Although we think of ourselves as the same person throughout life, the structural and functional state of the brain changes dramatically over the human lifespan. The initial development of the nervous system entails the generation and differentiation of neurons, the formation of axonal pathways, and the elaboration of vast numbers of synapses. Each of these events relies upon the interplay of secreted signals, their receptors, and transcriptional regulators, as well as adhesion and recognition molecules that determine appropriate identity, positions, and connections for developing neurons. The circuits that emerge from these processes mediate an increasingly complex array of behaviors. Subsequent experience during postnatal life—and the activity-dependent molecular mechanisms that translate experience into changes in neuronal growth and gene expression— continues to shape neural circuits, the related behavioral repertoires, and ultimately cognitive abilities. These changes are most pronounced during developmental windows in early life called critical periods. Even in maturity, however, synaptic connections can be modified as new skills and memories are acquired and older ones are forgotten; even some new neurons can be generated in a few specialized regions. Some of the mechanisms used during early development are evidently retained and adapted to mediate these ongoing changes in the mature brain.

Finally, like any other organ system, the brain is subject to disease and traumatic insults. Some of these processes call repair mechanisms into play; however, the capacity of the mature brain for repair or regeneration is limited. Diseases like amyotrophic lateral sclerosis, Parkinson's disease, and Alzheimer's disease all reflect pathologies of processes that normally contribute to neuronal development and to the subsequent maintenance and modification of neural circuitry.

Chapter 21



Early Brain Development

Overview

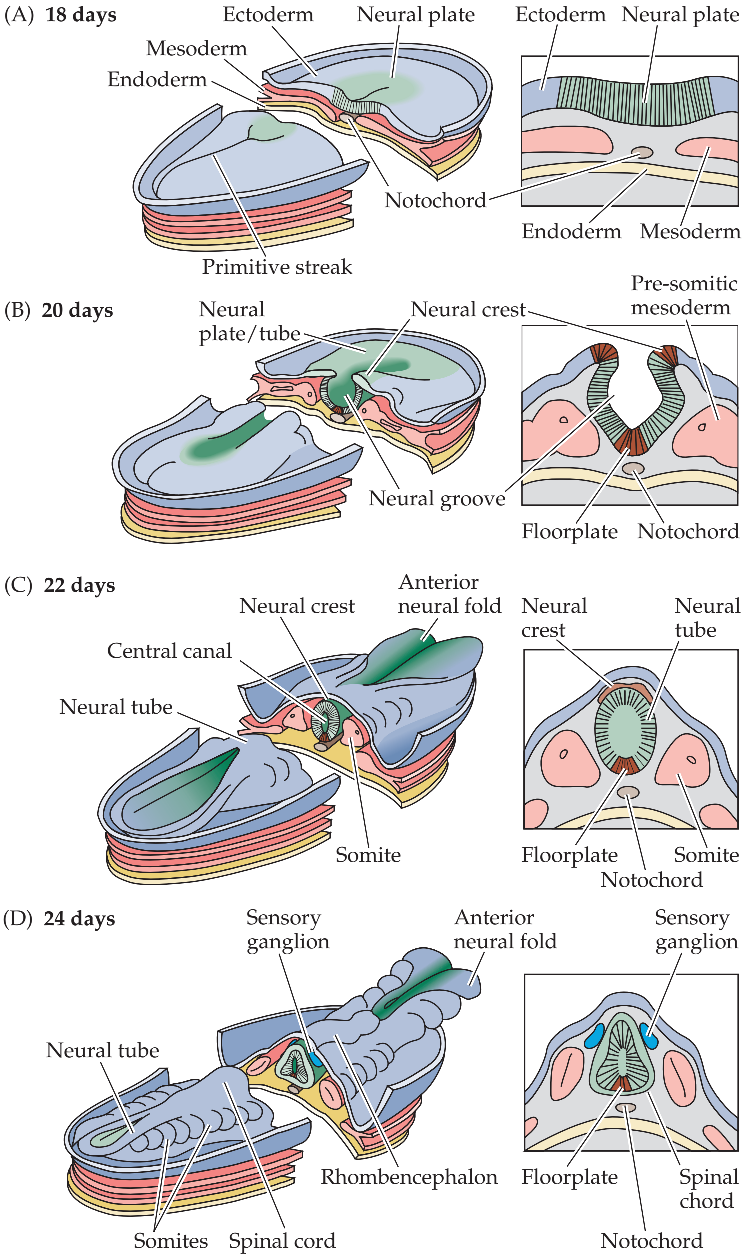
The elaborate architecture of the adult brain is the product of genetic instructions, cell-to-cell signals, and eventually interactions between the developing child and the external world. The early development of the nervous system is dominated by events that occur prior to the formation of synapses and are therefore activity-independent. These early events include the establishment of the primordial nervous system in the embryo, the initial generation of neurons from undifferentiated precursor cells, the formation of the major brain regions, and the migration of neurons from sites of generation to their final positions. These processes set the stage for the subsequent formation of axon pathways and synaptic connections. When any of these processes goes awry—because of genetic mutation, disease, or exposure to drugs or chemicals—the consequences can be disastrous. Indeed, most congenital brain defects result from interference with the normal mechanisms of activity-independent neuronal development. With the advent of powerful new techniques, the cellular and molecular machinery underlying these extraordinarily complex events is beginning to be understood.

The Initial Formation of the Nervous System: Gastrulation and Neurulation

Well before the patch of cells that will eventually become the brain and spinal cord appears, polarity (anterior versus posterior, medial versus lateral) and the primitive cell layers required for the subsequent formation of the nervous system are established in the embryo. Critical to this early framework in all vertebrate embryos is the process of **gastrulation**. This invagination of the developing embryo (which starts out as a single sheet of cells) produces the three primitive cell layers or **germ layers**: the outer layer, or **ectoderm**; the middle layer, or **mesoderm**; and the inner layer, or **endoderm** (Figure 21.1). Based on the position of the invaginating mesoderm and endoderm, gastrulation defines the midline, anterior–posterior, and dosal–ventral axes of all vertebrate embryos.

One key consequence of gastrulation is the formation of the **notochord**, a distinct cylinder of mesodermal cells that extends along the midline of the embryo from mid-anterior to posterior. The notochord forms from an aggregation of mesoderm that invaginates and extends inward from a surface indentation called the **primitive pit**, which subsequently elongates to form the **primitive streak**. As a result of these cell movements during gastrulation, the notochord comes to define the embryonic midline, and thus the major axis of symmetry for the entire body. The ectoderm that lies immediately above the notochord, called the **neuroectoderm**, gives rise to the entire nervous system.

Figure 21.1 Neurulation in the mammalian embryo. On the left are dorsal views of the embryo at several different stages of early development; each boxed view on the right is a midline cross section through the embryo at the same stage. (A) During late gastrulation and early neurulation, the notochord forms by invagination of the mesoderm in the region of the primitive streak. The ectoderm overlying the notochord becomes defined as the neural plate. (B) As neurulation proceeds, the neural plate begins to fold at the midline (adjacent to the notochord), forming the neural groove and ultimately the neural tube. The neural plate immediately above the notochord differentiates into the floorplate, whereas the neural crest emerges at the lateral margins of the neural plate (farthest from the notochord). (C) Once the edges of the neural plate meet in the midline, the neural tube is complete. The mesoderm adjacent to the tube then thickens and subdivides into structures called somites—the precursors of the axial musculature and skeleton. (D) As development continues, the neural tube adjacent to the somites becomes the rudimentary spinal cord, and the neural crest gives rise to sensory and autonomic ganglia (the major elements of the peripheral nervous system). Finally, the anterior ends of the neural plate (anterior neural folds) grow together at the midline and continue to expand, eventually giving rise to the brain.


(A) 18 days
Ectoderm
Neural plate
Mesoderm
Endoderm
Notochord
Primitive streak
Ectoderm
Neural plate
Endoderm
Mesoderm
(B) 20 days
Neural plate/tube
Neural crest
Pre-somitic mesoderm
Neural groove
Floorplate
Notochord
(C) 22 days
Neural crest
Anterior neural fold
Central canal
Neural tube
Somite
Neural crest
Neural tube
Floorplate
Notochord
Somite
(D) 24 days
Sensory ganglion
Anterior neural fold
Neural tube
Rhombencephalon
Somites
Spinal cord
Sensory ganglion
Floorplate
Spinal chord
Notochord

In addition to specifying the basic topography of the embryo and determining the position of the nervous system, the notochord is required for subsequent neural differentiation (see Figure 21.1). Thus, the notochord (along with the primitive pit) sends **inductive signals** to the overlying ectoderm that cause a subset of neuroectodermal cells to differentiate into neural precursor cells. During this process, called **neurulation**, the midline ectoderm that contains these cells thickens into a distinct columnar epithelium called the **neural plate**. The lateral margins of the neural plate then fold inward, eventually transforming the neural plate into a tube. This **neural tube** subsequently gives rise to the brain and spinal cord.

The progenitor cells of the neural tube are known as **neural precursor cells**. These precursors are dividing **neural stem cells** (Box A) that produce

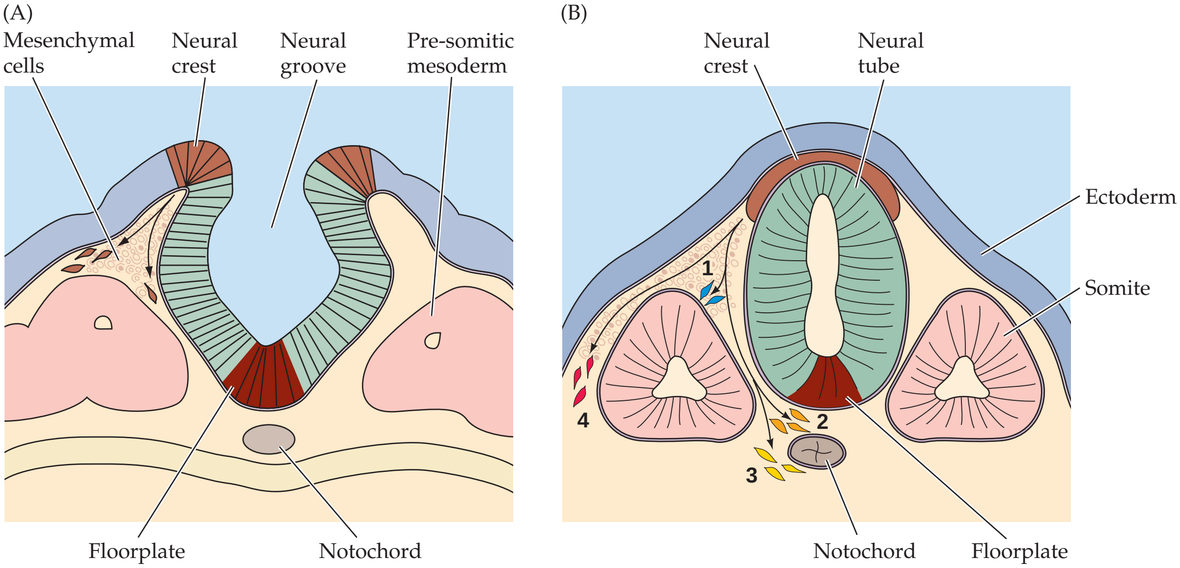


Figure 21.2 The neural crest. (A) Cross section through a developing mammalian embryo at a stage similar to that in Figure 21.1B. The neural crest cells are established based on their position at the boundary of the embryonic epidermis and neuroectoderm. Arrows indicate the initial migratory route of undifferentiated neural crest cells. (B) Four distinct migratory paths lead to differentiation of neural crest cells into specific cell types and structures. Cells that follow pathways (1) and (2) give rise to sensory and autonomic ganglia, respectively. The precursors of adrenal neurosecretory cells migrate along pathway (3) and eventually aggregate around the dorsal portion of the kidney. Cells destined to become non-neural tissues (for example, melanocytes) migrate along pathway (4). Each pathway permits the migrating cells to interact with different kinds of cellular environments, from which they receive inductive signals (see Figure 21.11). (After Sanes, 1988.)

more precursors, all with the capacity to give rise to neurons, astrocytes, and oligodendroglial cells. Eventually, subsets of these neural precursor cells will generate non-dividing **neuroblasts** that differentiate into neurons. Not all cells in the neural tube, however, are neural precursors. The cells at the ventral midline of the neural tube differentiate into a special strip of epithelial-like cells called the **floorplate (**reflecting their proximity to the notochord**)**, which provides molecular signals to specify the neuroblast cells. The position of the floorplate at the ventral midline defines the dorsoventral polarity of the neural tube and further influences the differentiation of neural precursor cells. Inductive signals from both the notochord and floorplate lead to differentiation of cells in the ventral portion of the neural tube that eventually give rise to spinal and hindbrain motor neurons (which are thus closest to the ventral midline). Precursor cells farther away from the ventral midline give rise to sensory relay neurons within the spinal cord and hindbrain.

At the most dorsal limit of the neural tube, a third population of cells emerges in the region where the edges of the folded neural plate join together. Because of their location, this set of precursors is called the **neural crest** (Figure 21.2). The neural crest cells migrate away from the neural tube through loosely packed mesenchymal cells that fill the spaces between the neural tube, embryonic epidermis, and somites. Subsets of neural crest cells follow specific pathways that expose them to additional inductive signals that influence their differentiation. As a result, neural crest cells give rise to a variety of progeny, including the neurons and glia of the sensory and visceral motor (autonomic) ganglia, the neurosecretory cells of the adrenal gland, and the neurons of the enteric nervous system. Neural crest cells also contribute to variety of non-neural structures such as pigment cells, cartilage, and bone, particularly in the face and skull.

The Molecular Basis of Neural Induction

The essential consequence of gastrulation and neurulation for the development of the nervous system is the emergence of a population of neural precursors from a subset of ectodermal cells. Through a variety of experimental manipulations, primarily involving extirpation or transplantation of differ-

Box A

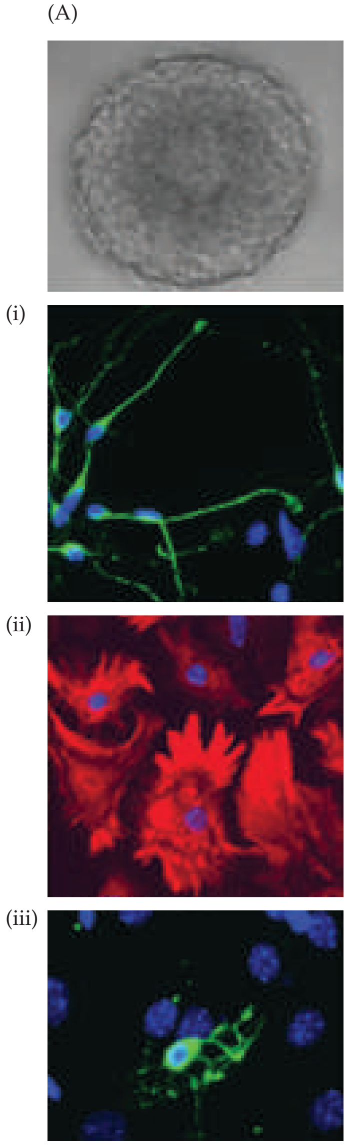
Stem Cells: Promise and Perils

One of the most highly publicized issues in biology over the past several years has been the use of stem cells as a possible way of treating a variety of neurodegenerative conditions, including Parkinson's, Huntington's, and Alzheimer's diseases. Amidst the social, political, and ethical debate set off by the promise of stem cell therapies, an issue that tends to get lost is what, exactly, is a stem cell?

Neural stem cells are an example of a broader class of stem cells called somatic stem cells. These cells are found in various tissues, either during development or in the adult. All somatic stem cells share two fundamental characteristics: they are self-renewing, and upon terminal division and differentiation they can give rise to the full range of cell classes within the relevant tissue.

Thus, a neural stem cell can give rise to another neural stem cell or to any of the main cell classes found in the central and peripheral nervous system (inhibitory and excitatory neurons, astrocytes, and oligodendrocytes; Figure A). A neural stem cell is therefore distinct from a progenitor cell, which is incapable of continuing self-renewal and usually has the capacity to give rise to only one class of differentiated progeny. An oligodendroglial progenitor, for example, continues to give rise to oligodendrocytes until its mitotic capacity is exhausted; a neural stem cell, in contrast, can generate more stem cells as well as a full range of differentiated neural cell classes, presumably indefinitely.

Neural stem cells, and indeed all classes of somatic stem cells, are distinct from embryonic stem cells. Embryonic stem cells (also known as ES cells) are derived from pre-gastrula embryos. ES cells also have the potential for infinite self-renewal and can give rise to all tissue and cell types throughout the organism including germ cells that can generate gametes (recall that somatic stem cells can only generate tissue specific cell types). There is some debate about the capacity of somatic stem cells to assume embryonic stem cell properties. Some experiments with hematopoetic and neural stem cells indicate that these cells can give rise to appropriately differentiated cells in other tissues; however, some of these experiments have not been replicated.

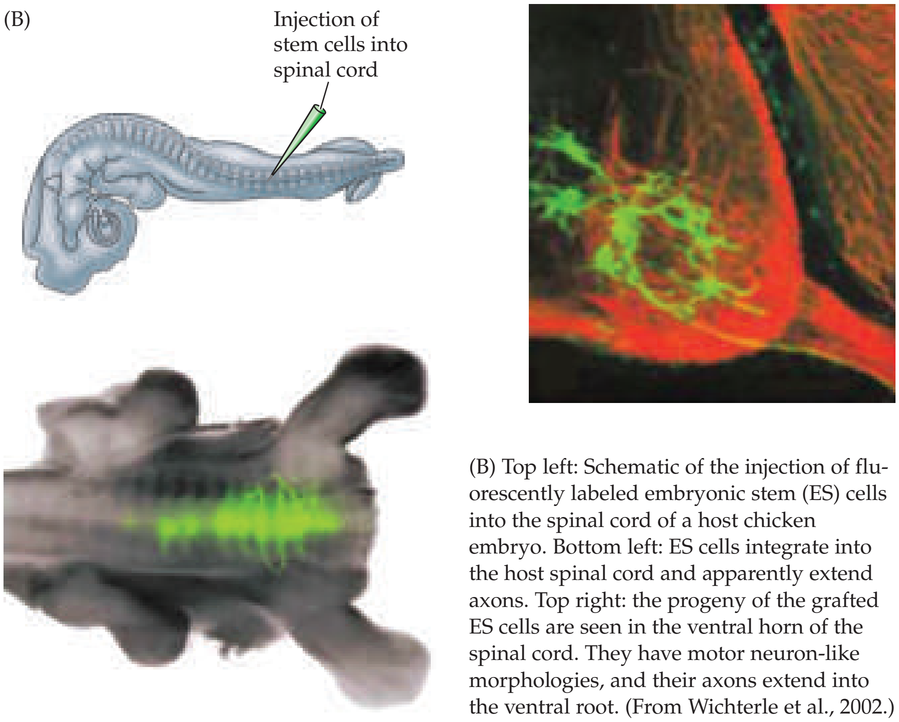


(A) A single "neurosphere" consisting of clonally related neural stem cells from the adult forebrain is shown at top. Neurosphere-derived stem cells can differentiate to produce (i) GABAergic neurons, (ii) astrocytes, and (iii) oligodendrogila.

The ultimate therapeutic promise of stem cells—neural or other types—is their ability to generate newly differentiated cell classes to replace those that may have been lost due to disease or injury. Such therapies have been imagined for some forms of diabetes (replacement of islet cells that secrete insulin) and some hematopoetic diseases. In the nervous system, stem cell therapies have been suggested for replacement of dopaminergic cells lost to Parkinson's disease and replacing lost neurons in other degenerative disorders.

While intriguing, this projected use of stem cell technology raises some significant perils. These include insuring the controlled division of stem cells when introduced into mature tissue, and identifying the appropriate molecular instructions to achieve differentiation of the desired cell class. Clearly, the latter challenge will need to be met with a fuller understanding of the signaling and transcriptional regulatory steps used during development to guide differentiation of relevant neuron classes in the embryo.

At present, there is no clinically validated use of stem cells for human therapeutic applications in the nervous system. Nevertheless, some promising work in mice and other experimental animals indicates that both somatic and ES cells can acquire distinct identities if given appropriate instructions in vitro (i.e., prior to introduction into the host), and if delivered into a supportive host environment. For example, ES cells grown in the presence of platelet-derived growth factor, which biases progenitors toward glial fates, can generate oligodendroglial cells that can myelinate axons in myelin-deficient rats. Similarly, ES cells pretreated with retinoic acid matured into motor neurons when introduced into the



(B) Top left: Schematic of the injection of fluorescently labeled embryonic stem (ES) cells into the spinal cord of a host chicken embryo. Bottom left: ES cells integrate into the host spinal cord and apparently extend axons. Top right: the progeny of the grafted ES cells are seen in the ventral horn of the spinal cord. They have motor neuron-like morphologies, and their axons extend into the ventral root. (From Wichterle et al., 2002.)

developing spinal cord (Figure B). While such experiments suggest that a combination of proper instruction and correct placement can lead to appropriate differentiation, there are still many issues to be resolved before the promise of stem cells for nervous system repair becomes a reality.

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ent portions of developing embryos, embryologists recognized early on that this process depends on signals arising from cells in the primitive pit and notochord. Because a wide variety of chemical agents and physical manipulations are able to mimic some of the effects of these endogenous signals, their nature remained a mystery for several decades. It is now clear that the generation of cell identity—of which neural induction is but one mechanism—results from the spatial and temporal control of different sets of genes by endogenous signaling molecules (Figure 21.3). These inducing signals—including those from the primitive pit and notochord—are, not surprisingly, molecules that modulate gene expression. The increasingly sophisticated effort to understand exactly how these inductive signals work has therefore focused on molecules that can modify patterns of gene expression.

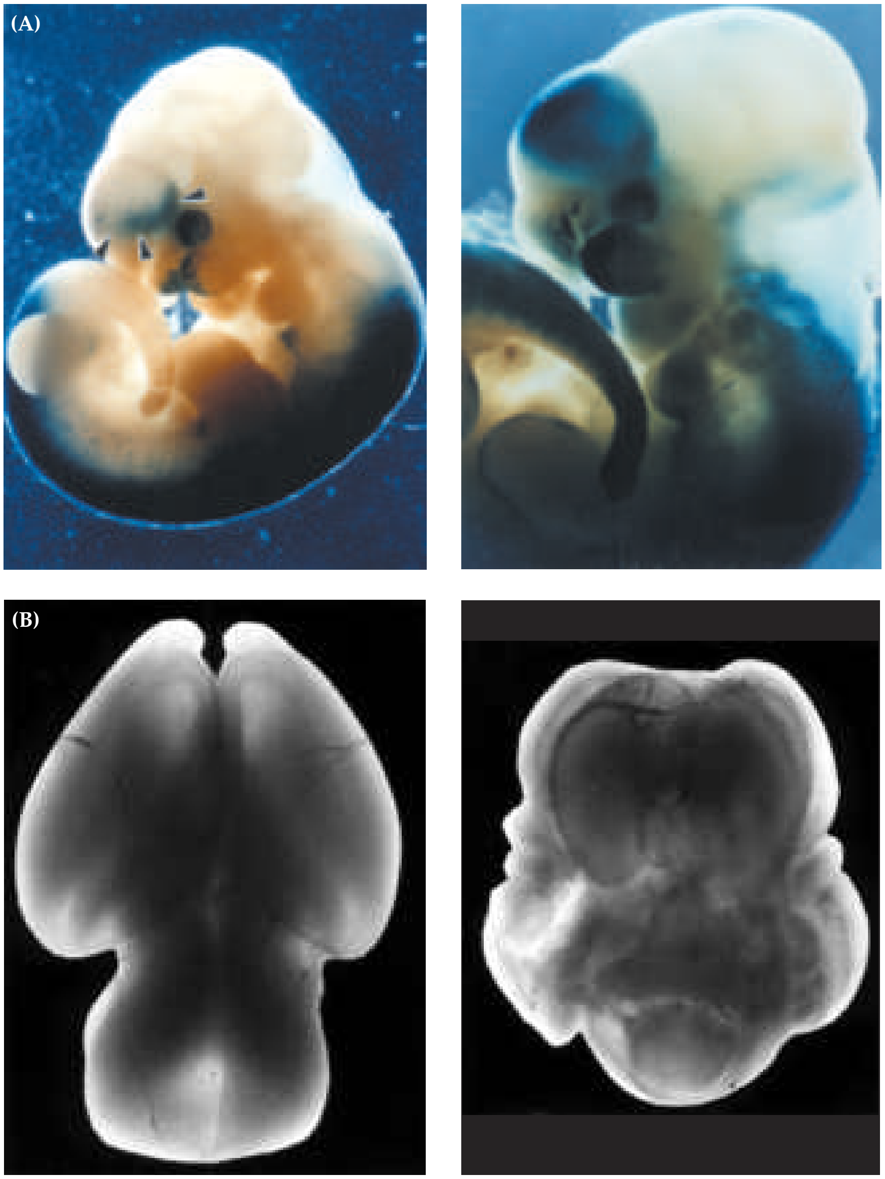
One of the first of these inductive signals to be identified was **retinoic acid**, a derivative of vitamin A and a member of the steroid/thyroid superfamily of hormones (Figure 21.3 and Box B). Retinoic acid activates a unique class of **transcription factors**—the **retinoid receptors**—that modulate the expression of a number of target genes. Peptide hormones provide another class of inductive signals, including those that belong to the **fibroblast growth factor** (**FGF**) and **transforming growth factor** (**TGF**) families. Within the TGF family, the **bone morphogenetic proteins** (**BMPs**) are particularly important for a variety of events in neural induction and differentiation; these will be dis-

Box B

Retinoic Acid: Teratogen and Inductive Signal

In the early 1930s, investigators noticed that vitamin A deficiency during pregnancy in animals led to a variety of fetal malformations. The most severe abnormalities affected the developing brain, which was often grossly malformed. At about the same time, experimental studies yielded the surprising finding that *excess* vitamin A caused similar defects. These observations suggested that a family of compounds—metabolic precursors or derivatives of vitamin A called retinoids—are teratogenic. (*Teratogenesis* is the term for birth defects induced by exogenous agents.) The retinoids include the alcohol form of vitamin A (retinol), the aldehyde form (retinal), and the acid form (retinoic acid). Subsequent experiments in animals confirmed that other retinoids produce birth defects similar to those generated by too much—or too little—vitamin A. The disastrous consequences of exposure to exogenous retinoids during human pregnancy were underscored in the early 1980s when the drug Accutane® (the trade name for isoretinoin, or 13-*cis*-retinoic acid) was introduced as a treatment for severe acne. Women who took this drug during pregnancy had an increased number of spontaneous abortions and children born with a range of birth defects. Despite the importance of these several findings, the reasons for the adverse effects of retinoids on fetal development remained obscure well into the late twentieth century.

An important insight into teratogenic potential of retinoids came when embryologists working on limb development in chicks found that retinoic acid mimics the inductive ability of tissues in the limb bud. Still the mystery remained as to just what retinoic acid (or its absence) was doing to influence or compromise development. An important answer came in the mid-1980s, when the receptors for retinoic acid were discovered. These receptors are members of the steroid/thyroid hormone receptor superfamily; when they bind retinoic acid or similar ligands, the receptors act as transcription factors to activate specific genes. Furthermore, careful biochemical analysis showed that retinoic acid was synthe-



(A) At left, retinoic acid activates gene expression in a subset of cells in the normal developing forebrain of a mid-gestation mouse embryo (blue areas indicate β-galactosidase reaction product, an indicator of gene expression in this experiment). At right, after maternal ingestion of a small quantity of retinoic acid (0.00025 mg/g of maternal weight), gene expression is ectopically activated throughout the forebrain. (B) At left, the brain of a normal mouse at term; at right, the grossly abnormal brain of a mouse whose mother ingested this same amount of retinoic acid at mid-gestation. (A from Anchan et al., 1997; B from Linney and LaMantia, 1994.)

sized by embryonic tissues. Subsequent studies have shown that retinoic acid activates gene expression at several sites in the embryo including the developing brain (see figure). Among the most important targets for retinoic acid regulation are genes for other inductive signals including sonic hedgehog and Hox genes (see Box C). Thus, an excess or deficiency of retinoic acid can disrupt normal development by eliciting inappropriate patterns of retinoid-induced gene expression.

The role of retinoic acid as both a teratogen and an endogenous signaling molecule implies that the retinoids cause birth defects by mimicking the normal signals that influence gene expression. The story provides a good example of how teratogenic, clinical, cellular, and molecular observations can be combined to explain seemingly bizarre developmental pathology.

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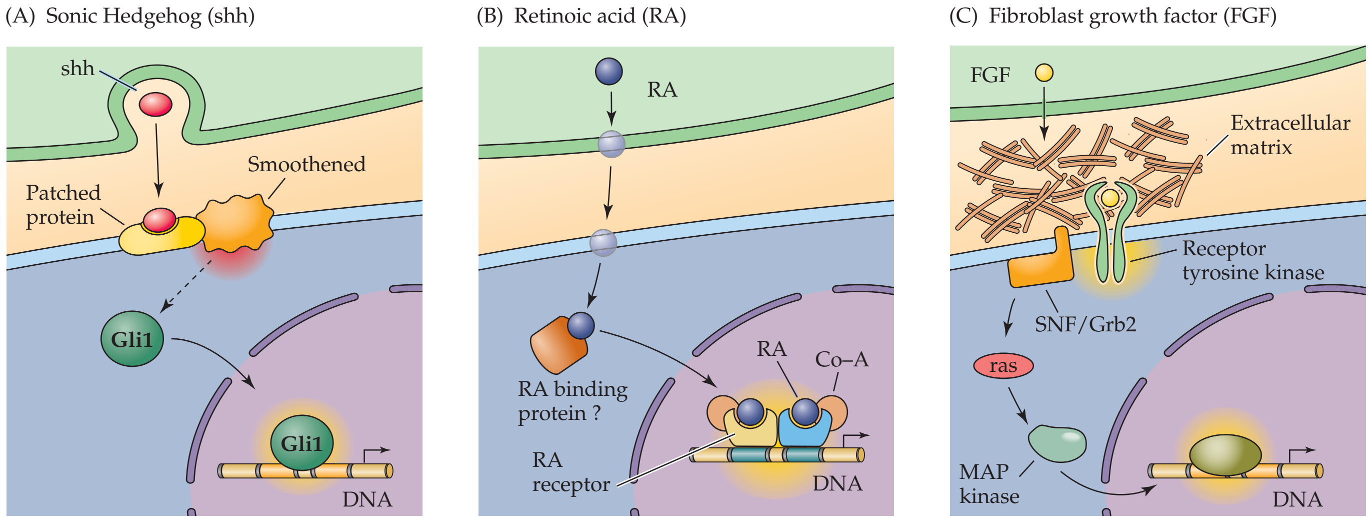
cussed in more detail later in this chapter. Another peptide hormone essential for neural induction is **sonic hedgehog** (**shh**). Shh is thought to be particularly important for differentiation of neurons—including motor neurons—in the ventral portion of the neural tube. Finally, members of the **Wnt** family of secreted signals (vertebrate homologues of the *wingless* gene of *Drosophila*) can modulate several aspects of neural induction and differentiation including some aspects of neural crest differentiation. Each of these molecules is produced by a variety of embryonic tissues—including the notochord, the floorplate, and the neural ectoderm itself, as well as tissues like somites that are adjacent to the developing nervous system—and they bind to surface receptors on nearby cells. In some cases, these signals have graded effects based upon the distance of target cells from the source of the inductive signal. These effects may represent a diffusion gradient of the signal, or graded activity due to distribution of receptors or other signaling components. Other signals are more specific in their action, being most effective at the boundaries between distinct cell populations. The results of inductive signaling include changes in shape, motility, and gene expression in the target cells.

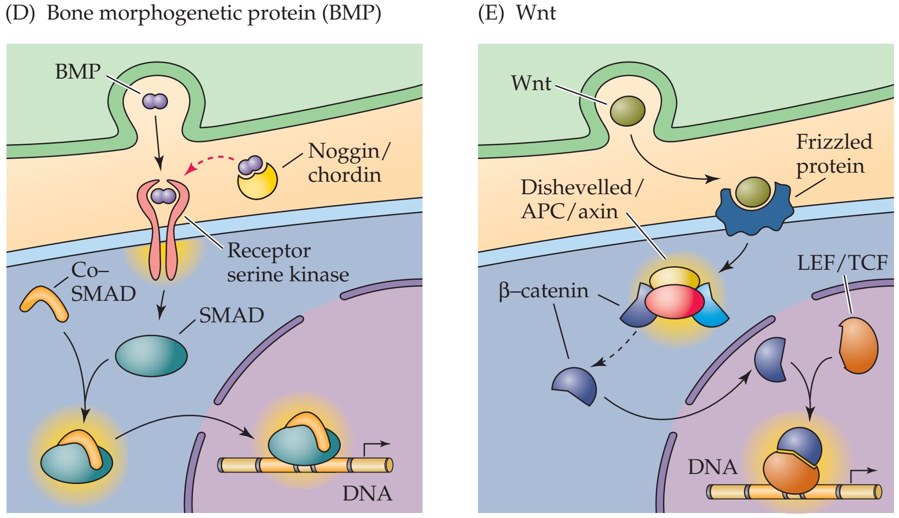
The receptors for inductive signals, their locations, and their mode of action are clearly essential elements in determing the consequences of inductive signaling (Figure 21.3). The receptors for the FGF and BMP families of peptide signals are protein kinases. FGF receptors are tyrosine kinases that bind FGF with the cooperation of extracellular matrix components including heparan sulfate proteoglycan. Upon binding, activation of the intracellular kinase domains of the FGF receptors leads to activation of the RAS/MAP kinase pathway (see Chapter 7). This signaling can modify cytoskeletal and cytoplasmic components and thus alter the shape or motility of a cell, or it can in regulate gene expression, particularly genes that influence cell proliferation. BMP receptors are serine threonine kinases that phosphorylate a group of cytoplasmic proteins called SMADs. Upon phosphorylation, SMAD multimers translocate to the nucleus and interact with other DNA-binding proteins, thus modulating gene expression.


(A) Sonic Hedgehog (shh)

(B) Retinoic acid (RA)

(C) Fibroblast growth factor (FGF)

shh
Smoothened
Patched protein
Gli1
Gli1
DNA
RA
RA binding protein ?
RA
Co–A
RA receptor
DNA
FGF
Extracellular matrix
Receptor tyrosine kinase
SNF/Grb2
ras
MAP kinase
DNA


(D) Bone morphogenetic protein (BMP)

(E) Wnt

BMP
Noggin/ chordin
Receptor serine kinase
Co– SMAD
SMAD
DNA
Wnt
Frizzled protein
Dishevelled/ APC/axin
LEF/TCF
β–catenin
DNA

Figure 21.3 Major inductive signaling pathways in vertebrate embryos. Schematics of ligands, receptors, and primary intracellular signaling molecules for retinoic acid (RA); members of the FGF and TGF-β superfamily of peptide hormones; sonic hedgehog (shh); and the Wnt family of signals. Each of these pathways contributes to the initial establishment of the neural ectoderm, as well as to the subsequent differentiation of distinct classes of neurons and glia throughout the brain.

Some inductive signals use more indirect signaling routes. For example, the transduction of signals via sonic hedgehog depends on the cooperative binding of two surface receptors followed by internalization of the receptor. The internalized complexes influence nuclear translocation of transcription factors (including Gli1) and subsequent modulation of gene expression. The transduction of Wnt signals has a similarly circuitous route, leading ultimately to the nucleus. Wnt receptors, including a family of proteins with the fanciful name "frizzled," initiate a cascade of events after Wnt binding that leads to the degradation of a cytoplasmic protein complex that normally prevents the translocation of β-catenin from the cytoplasm to the nucleus. Once freed from this inhibition, β-catenin enters the nucleus and influences expression of a number of downstream genes.

A particularly distinctive aspect neural induction is the mechanism by which the BMPs influence neural differentiation (see Figure 21.3). As the name suggests, these peptide hormones, which are members of the TGF-β family, elicit osteogenesis from mesodermal cells. If ectodermal cells are exposed to BMPs, they assume an epidermal fate. But how then does the ectoderm manage to become neuralized, given the fact that BMPs are produced by the somites and surrounding mesodermal tissue? All of these structures are in position to signal to the neuroectoderm, and therefore to convert it to epidermis. This fate is evidently avoided in the neural plate by the local activity of other inductive signaling molecules such as noggin and chordin—two members of a broad class of endogenous antagonists that modulate signaling via the TGF-β family (including that of the BMPs). Both of these molecules bind directly to the BMPs and thus prevent their binding to BMP receptors. In this way, the neuroectoderm is "rescued" from becoming epidermis. Such negative regulation has reinforced the speculation that becoming a neuron is actually the "default" fate for embryonic ectodermal cells.

Some of these molecular signals have been implicated in determining the fates of specific classes of cells in the developing nervous system act after the initial differentiation of the neural plate, tube and neural crest (Figure 21.4). As mentioned above, sonic hedgehog (shh) is essential for the differentiation of motor neurons in the ventral spinal cord (Figure 21.4D), as well as some classes of neurons and glia in the forebrain; TGF-β family signals (including the BMPs) are important for the establishment of dorsal cells in the spinal cord—as well as the neural crest—and can influence other neuron classes in dorsal positions throughout the forebrain. The Wnt family of signals also is essential for the differentiation of neural crest, cerebellar granule cells, and

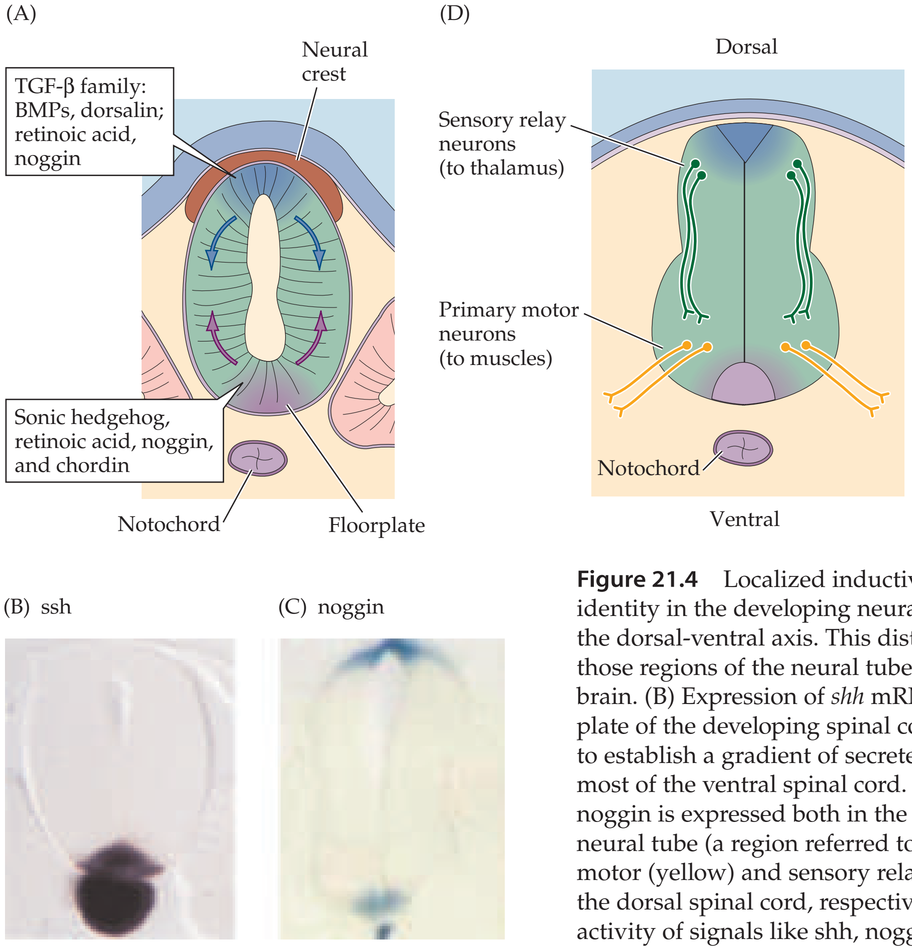

(A)
Neural crest
TGF-β family: BMPs, dorsalin; retinoic acid, noggin
Sonic hedgehog, retinoic acid, noggin, and chordin
Notochord
Floorplate
(D)
Dorsal
Sensory relay neurons (to thalamus)
Primary motor neurons (to muscles)
Notochord
Ventral
(B) ssh
(C) noggin

Figure 21.4 Localized inductive signals influence axes and cellular identity in the developing neural tube. (A) Local signals associated with the dorsal-ventral axis. This distribution of signaling molecules is seen in those regions of the neural tube that give rise to the spinal cord and hindbrain. (B) Expression of *shh* mRNA is limited to the notochord and floorplate of the developing spinal cord. This localized expression is thought to establish a gradient of secreted shh peptide extending throughout most of the ventral spinal cord. (C) The endogenous TGF-β antagonist noggin is expressed both in the notochord and in the dorsal medial neural tube (a region referred to as the roofplate). (D) The identity of motor (yellow) and sensory relay neurons (green) in the ventral versus the dorsal spinal cord, respectively, is thought to reflect the graded local activity of signals like shh, noggin, and others. This impression has been confirmed in studies that disrupt the balance of local inductive signals.

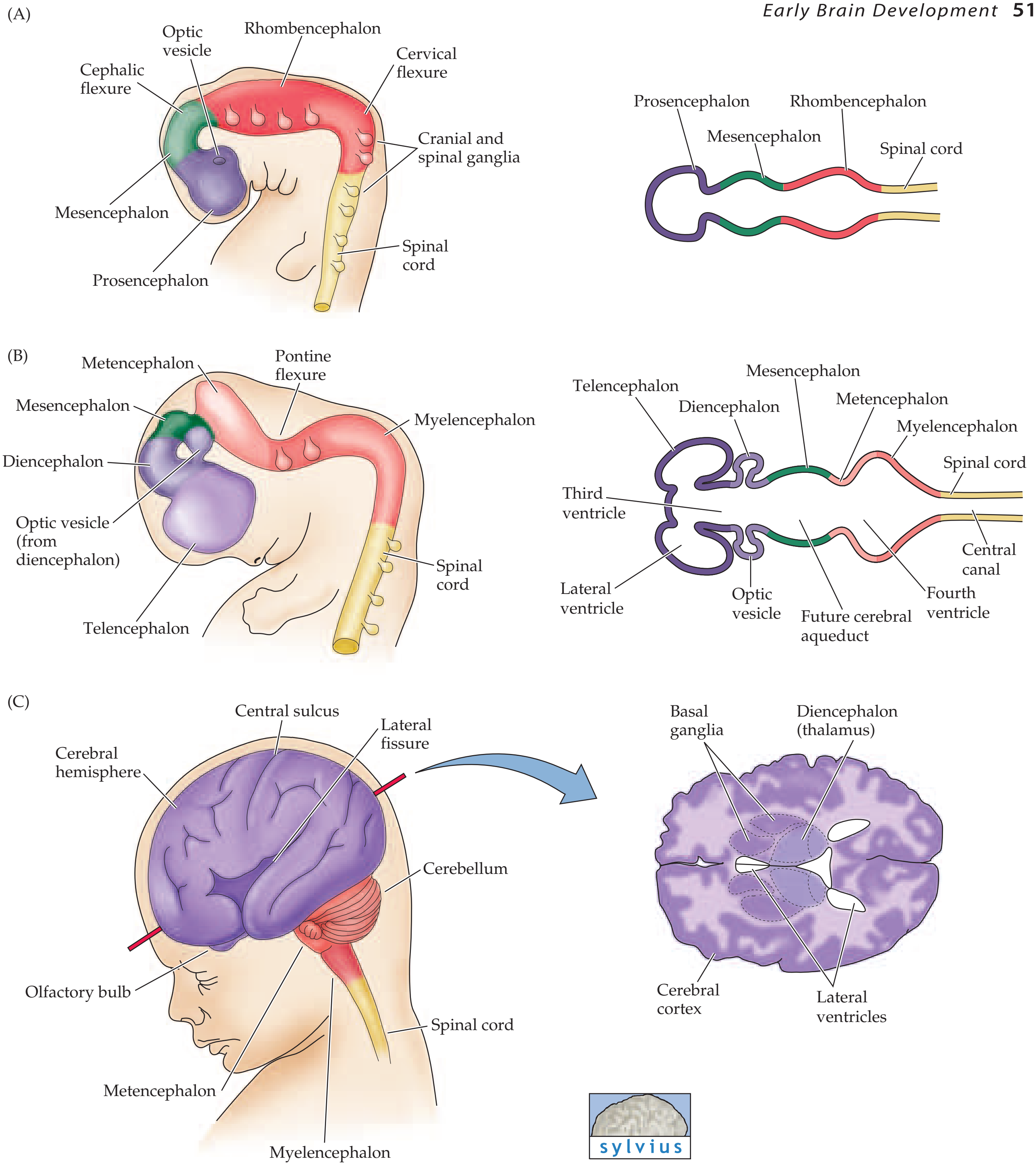
Figure 21.5 Regional specification of the developing brain. (A) Early in gestation the neural tube becomes subdivided into the prosencephalon (at the anterior end of the embryo), mesencephalon, and rhombencephalon. The spinal cord differentiates from the more posterior region of the neural tube. The initial bending of the neural tube at its anterior end leads to a cane shape. At right is a longitudinal section of the neural tube at this stage, showing the position of the major brain regions. (B) Further development distinguishes the telencephalon and diencephalon from the prosencephalon; two other subdivisions—the metencephalon and myelencephalon—derive from the rhombencephalon. These subregions give rise to the rudiments of the major functional subdivisions of the brain, while the spaces they enclose eventually form the ventricles of the mature brain. At right is a longitudinal section of the embryo at the developmental stage shown in (B). (C) The fetal brain and spinal cord are clearly differentiated by the end of the second trimester. Several major subdivisions, including the cerebral cortex and cerebellum, are clearly seen from the lateral surfaces. At right is a cross section through the forebrain at the level indicated showing the nascent sulci and gyri of the cerebral cortex, as well as the differentiation of thalamic nuclei. ▶

forebrain neurons. Thus, inductive signals can serve multiple purposes throughout neural development.

Awareness of the molecules involved in neural induction has provided a much more informed way of thinking about the etiology and prevention of a number of congenital disorders of the nervous system. Anomalies like **spina bifida** (failure of the posterior neural tube to close completely), **anencephaly** (failure of the anterior neural tube to close at all), **holoprosencephaly** (disrupted regional differentiation of the forebrain), and other brain malformations (often accompanied by mental retardation) can result from environmental insults that disrupt inductive signaling or from the mutation of genes that participate in this process. As already described, excessive intake of vitamin A can impede neural tube closure and differentiation or disrupt later aspects of neuronal differentiation (see Box B). Embryonic exposure to a variety of other drugs—alcohol and thalidomide are good examples—can also elicit pathological differentiation of the embryonic nervous system by providing inductive signals at inappropriate times or places. Altered cholesterol metabolism can compromise sonic hedgehog signaling. Furthermore, dietary insufficiency of substances such as folic acid can disrupt neural tube formation by compromising cellular mechanisms essential for normal cell division and motility. Because the consequences of disordered neural induction are so severe, pregnant women are well advised to avoid virtually all drugs and dietary supplements except those specifically prescribed by a physician, especially during the first trimester of pregnancy.

Formation of the Major Brain Subdivisions

Soon after neural tube formation, the forerunners of the major brain regions become apparent as a result of morphogenetic movements that bend, fold, and constrict the neural tube. Initially, the anterior end of the tube forms a crook, giving it the shape of a cane handle (Figure 21.5A). The end of the cane nearest the sharper bend, the **cephalic flexure**, balloons out to form the **forebrain**, or **prosencephalon**. The **midbrain**, or **mesencephalon**, forms as a bulge above the cephalic flexure. The **hindbrain**, or **rhombencephalon**, forms in the long, relatively straight stretch between the cephalic flexure and the more caudal **cervical flexure**. Caudal to the cervical flexure, the neural tube forms the precursor of the spinal cord. This bending and folding con-


(A)
Optic vesicle
Rhombencephalon
Cephalic flexure
Cervical flexure
Cranial and spinal ganglia
Mesencephalon
Spinal cord
Prosencephalon
Prosencephalon
Rhombencephalon
Mesencephalon
Spinal cord
(B)
Metencephalon
Pontine flexure
Mesencephalon
Myelencephalon
Diencephalon
Optic vesicle (from diencephalon)
Spinal cord
Telencephalon
Mesencephalon
Telencephalon
Diencephalon
Metencephalon
Myelencephalon
Spinal cord
Third ventricle
Central canal
Lateral ventricle
Optic vesicle
Future cerebral aqueduct
Fourth ventricle
(C)
Central sulcus
Lateral fissure
Cerebral hemisphere
Cerebellum
Olfactory bulb
Spinal cord
Metencephalon
Myelencephalon
Basal ganglia
Diencephalon (thalamus)
Cerebral cortex
Lateral ventricles
sylvius

stricts or enlarges the lumen enclosed by the developing neural tube. These lumenal spaces eventually become the ventricles of the mature brain (Figure 21.5B; see also Appendix B).

Once the primitive brain regions are established in this way, they undergo at least two more rounds of partitioning, each of which produces additional regions in the adult (Figure 21.5C). Thus, the lateral aspects of the rostral prosencephalon forms the **telencephalon**. The two bilaterally symmetric telencephalic vesicles include dorsal and ventral territories. The dorsal terri-

Box C

Homeotic Genes and Human Brain Development

The notion that particular genes can influence the establishment of distinct regions in an embryo arose from efforts to catalog single-gene mutations that affect development of the fruit fly *Drosophila*. In the 1960s and 1970s, E. B. Lewis at the California Institute of Technology reported a number of mutations that resulted in either the duplication of a distinct body segment or the appearance of an inappropriate structure at an ectopic location in the fly. These genes were called homeotic genes because they were able to convert segments of one sort to those of another (*homeo* is Greek for "similar"). Subsequently, studies by C. Nusslein-Volhard and E. Wieschaus demonstrated the existence of numerous such "master control" genes, each forming part of a cascade of gene expression leading to the distinctive segmentation of the developing embryo. (In 1995, Lewis, Nusslein-Volhard, and Wieschaus shared a Nobel Prize for these discoveries.)

Homeotic genes code for DNA-binding proteins—that is, transcription factors—that bind to a particular sequence of genomic DNA called the "homeobox." Similar genes have been found in most species, including humans. Using an approach known as cloning by homology, at least four "clusters" of homeobox genes have been identified in virtually all vertebrates that have been examined. The genes of each cluster are closely, but not consecutively, spaced on a single chromosome. Other motifs identified in *Drosophila* have led to the discovery of additional families of DNA-binding proteins, which have again been found in a variety of species.

Importantly, a number of developmental anomalies in mice and humans have been associated with mutations in the homeotic or other developmental control genes initially identified in the fly. Relatively rare diseases like aniridia, Waardenburg syndrome, and Greig cephalopolysyndactyly syndrome (all disorders that disrupt the nervous system and peripheral structures like the iris or the digits) have been associated with human genes that are homologues of *Drosophila* developmental control genes. In addition, several other developmental disorders including autism and various forms of mental retardation can be associated with mutations or polymorphisms of homeobox genes (see text). Thus, the initial insights into the molecular control of development gleaned from genetic studies of *Drosophila* have opened new avenues for exploring the molecular basis of developmental disorders in humans.

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tory will give rise to the rudiments of the cerebral cortex and hippocampus, while the ventral territory gives rise to the basal ganglia (derived from embryonic structures called the **ganglionic eminences**), basal forebrain nuclei, and olfactory bulb. The more caudal portion of the prosencephalon forms the **diencephalon**, which contains the rudiments of the thalamus and hypothalamus, as well as a pair of lateral outpocketings (the **optic cups**) from which the neural portion of the retina will form. The dorsal portion of the mesencephalon gives rise to the superior and inferior colliculi, while the ventral portion gives rise to a collection of nuclei known as the midbrain tegmentum. The rostral part of the rhombencephalon becomes the **metencephalon** and gives rise to the adult cerebellum and pons. Finally, the caudal part of the rhombencephalon becomes the **myelencephalon** and gives rise to the adult medulla.

How can a simple tube of neuronal precursor cells produce such a variety of brain structures? At least part of the answer comes from the observation made early in the twentieth century that much of the neural tube is organized into repeating units called **neuromeres**. This discovery led to the idea

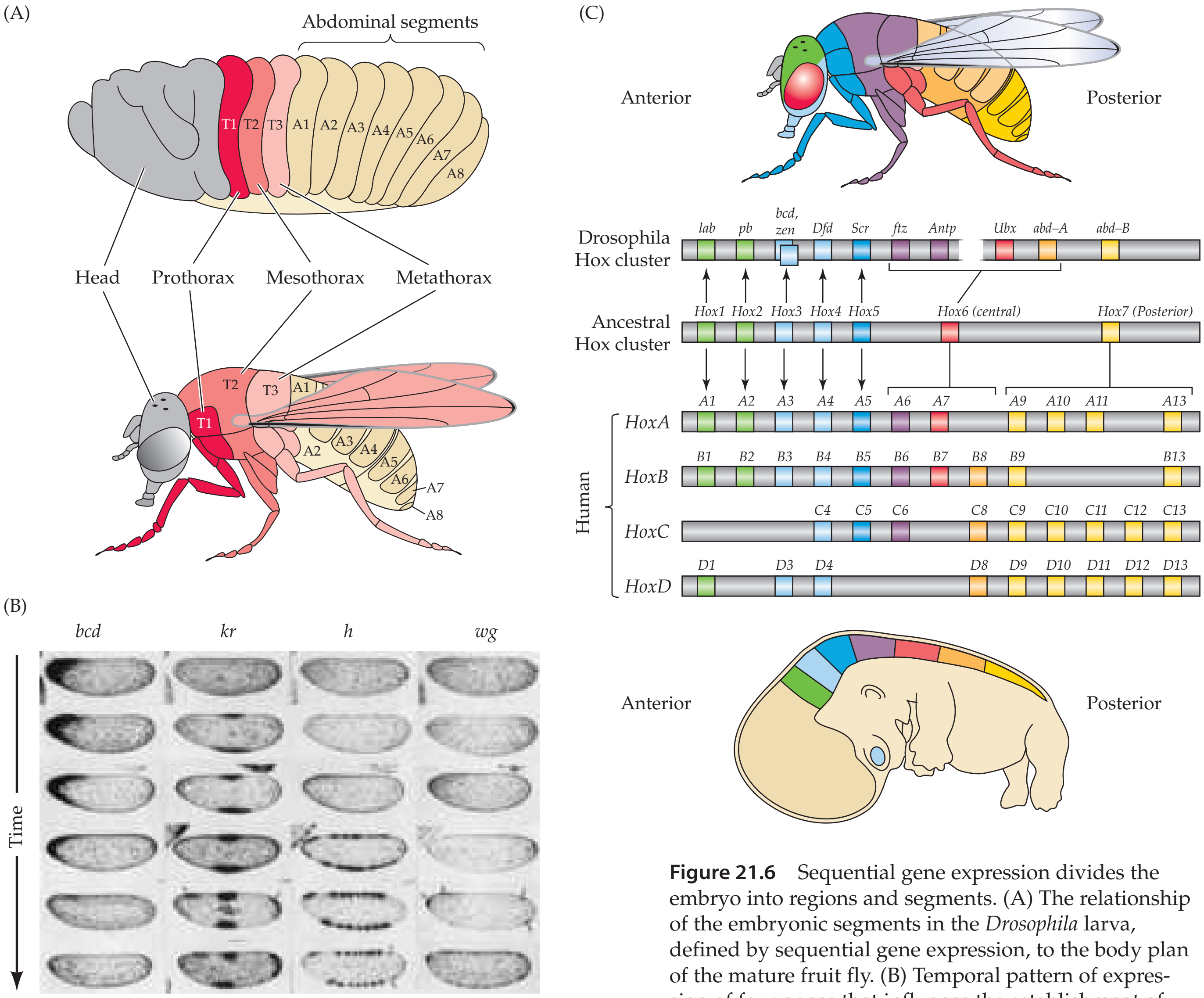

(A)
Abdominal segments
T1
T2
T3
A1
A2
A3
A4
A5
A6
A7
A8
Head
Prothorax
Mesothorax
Metathorax
(B)
bcd
kr
h
wg
Time
(C)
Anterior
Posterior
Drosophila Hox cluster
lab
pb
bcd, zen
Dfd
Scr
ftz
Antp
Ubx
abd–A
abd–B
Ancestral Hox cluster
Hox1
Hox2
Hox3
Hox4
Hox5
Hox6 (central)
Hox7 (Posterior)
Human
HoxA
A1
A2
A3
A4
A5
A6
A7
A9
A10
A11
A13
HoxB
B1
B2
B3
B4
B5
B6
B7
B8
B9
B13
HoxC
C4
C5
C6
C8
C9
C10
C11
C12
C13
HoxD
D1
D3
D4
D8
D9
D10
D11
D12
D13
Anterior
Posterior

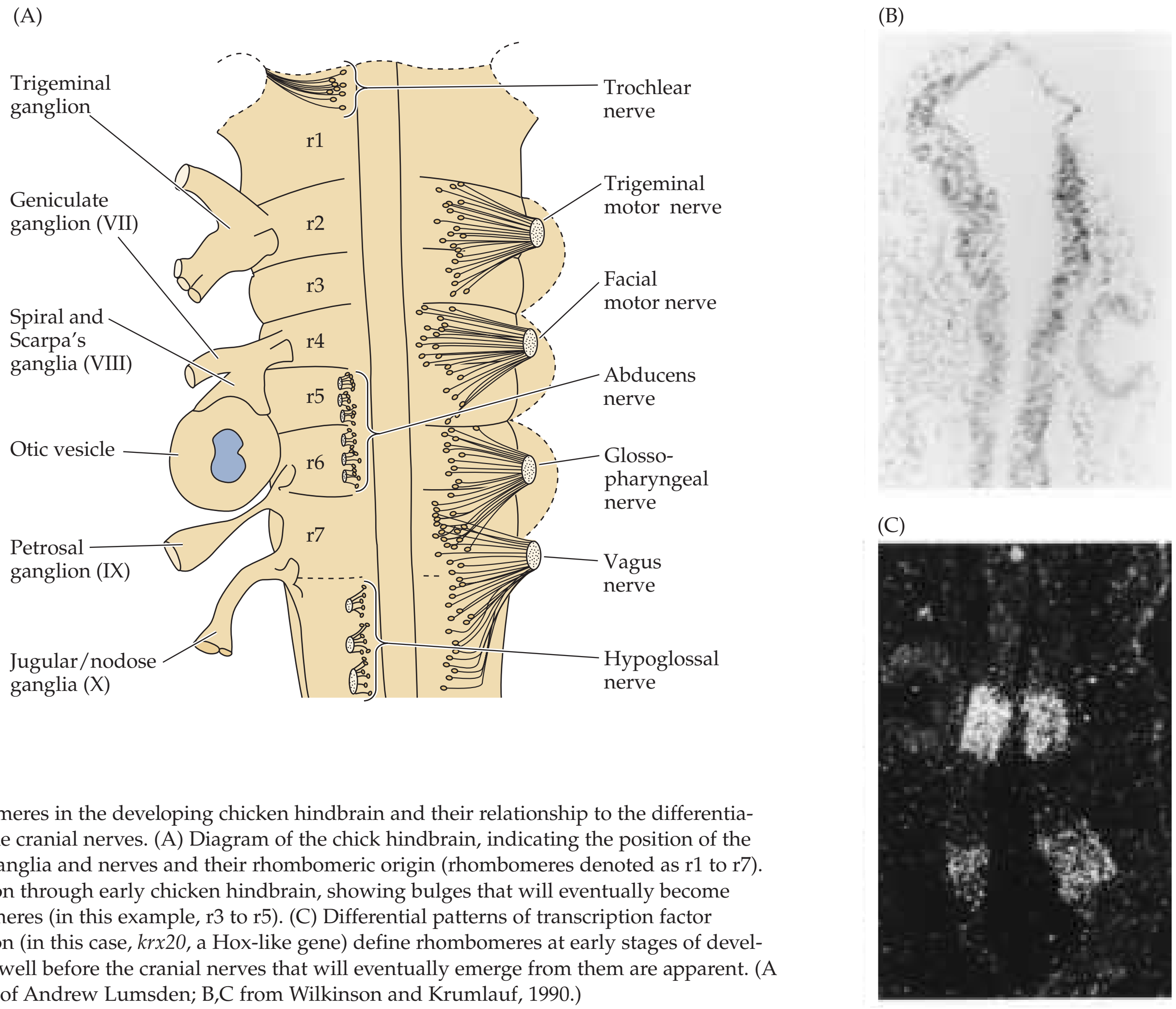
Figure 21.6 Sequential gene expression divides the embryo into regions and segments. (A) The relationship of the embryonic segments in the *Drosophila* larva, defined by sequential gene expression, to the body plan of the mature fruit fly. (B) Temporal pattern of expression of four genes that influence the establishment of the body plan in *Drosophila*. A series of sections through the anterior-posterior midline of the embryo are shown from early to later stages of development (top to bottom in each row). Initially, expression of the gene *bicoid* (*bcd*) helps define the anterior pole of the embryo. Next, *krüppel* (*kr*) is expressed in the middle and then at the posterior end of the embryo, defining the anterior-posterior axis. Then *hairy* (*h*) is expressed, which helps to delineate the domains that will eventually form the mature segmented body of the fly. Finally, the *wingless* (*wg*) gene is expressed, further refining the organization of individual segments. (C) Parallels between *Drosophila* segmental genes (the inferred "ancestral" homeobox genes from which invertebrate and vertebrate segmental genes evolved) and human Hox genes. Human Hox genes have apparently been duplicated twice, leading to four independent groups, each on a distinct human chromosome. The anterior-to-posterior pattern of Hox gene expression in both flies and mammals (including humans) follows the 3′-to-5′ orientation of these genes on their respective chromosomes. (A after Gilbert, 1994, and Lawrence, 1992; B from Ingham, 1988; C after Veraksa and Mc Ginnis, 2000.)

that the process of segmentation—used by all animal embryos at the earliest stages of development to establish regional identity in the body—might also establish regional identity in the developing brain. Enthusiasm for this hypothesis was stimulated by observations of the development of the body plan of the fruit fly *Drosophila*. In the fly, early expression of a class of genes called **homeotic** or **homeobox genes** (Box C) guides the differentiation of the embryo into distinct segments that give rise to the head, thorax, and abdomen (Figure 21.6). These genes code for DNA-binding proteins that can modulate the expression of other genes. Similar homeobox genes in mammals (referred to as **Hox genes**) have also been identified. In some cases their pattern of expression coincides with, or even precedes, the formation of morphological features such as the various bends, folds, and constrictions that signify the progressive regionalization of the developing neural tube, particularly in the hindbrain and spinal cord (Figure 21.6 and Box D).

Box D
Rhombomeres

An interesting parallel between early embryonic segmentation and early brain development was noticed around the turn of the nineteenth century. Several embryologists reported repeating units in the early neural plate and neural tube, which they called *neuromeres*. In the late 1980s, A. Lumsden, R. Keynes, and their colleagues, as well as R. Krumlauf, R. Wilkinson, and colleagues, noticed further that combinations of homeobox (Hox) and related genes (see Box C) are expressed in banded patterns in the developing chick nervous system, especially in the hindbrain (the common name for the rhombencephalon and its derivatives). These expression domains defined rhombomeres, which in the chick (as well as in most mammals), are a series of seven transient bulges in the developing rhombencephalon corresponding to the neuromeres described earlier. Rhombomeres are sites of differential cell proliferation (cells at rhombomere boundaries divide faster than cells in the rest of the rhombomere), differential cell mobility (cells from any one rhombomere cannot easily cross into adjacent rhombomeres), and differential cell adhesion (cells prefer to stick to those of their own rhombomere).

Later in development, the pattern of axon outgrowth from the cranial motor nerves also correlates with the earlier rhombomeric pattern. Cranial motor nerves (see Appendix A) originate either from a single rhombomere or from specific pairs of neighboring rhombomeres (transplantation experiments indicate that rhombomeres are in fact specified in pairs). Thus, *Hox* gene expression probably represents an early step in the forma-


(A)
Trigeminal ganglion
Geniculate ganglion (VII)
Spiral and Scarpa's ganglia (VIII)
Otic vesicle
Petrosal ganglion (IX)
Jugular/nodose ganglia (X)
r1
r2
r3
r4
r5
r6
r7
Trochlear nerve
Trigeminal motor nerve
Facial motor nerve
Abducens nerve
Glosso-pharyngeal nerve
Vagus nerve
Hypoglossal nerve
(B)
(C)

Rhombomeres in the developing chicken hindbrain and their relationship to the differentiation of the cranial nerves. (A) Diagram of the chick hindbrain, indicating the position of the cranial ganglia and nerves and their rhombomeric origin (rhombomeres denoted as r1 to r7). (B) Section through early chicken hindbrain, showing bulges that will eventually become rhombomeres (in this example, r3 to r5). (C) Differential patterns of transcription factor expression (in this case, *krx20*, a Hox-like gene) define rhombomeres at early stages of development, well before the cranial nerves that will eventually emerge from them are apparent. (A courtesy of Andrew Lumsden; B,C from Wilkinson and Krumlauf, 1990.)

tion of cranial nerves in the developing brain. Mutation or ectopic activation of Hox genes in mice alters the position of specific cranial nerves, or prevents their formation. Mutation of the *HoxA-1* gene by homologous recombination—the so-called "knockout" strategy for targeting mutations to specific genes—prevents normal formation of rhombomeres. In these animals, development of the external, middle, and inner ear is also compromised, and cranial nerve ganglia are fused and located incorrectly. Conversely, when the *HoxA-1* gene is expressed in a rhombomere where it is usually not seen, the ectopic expression causes changes in rhombomere identity and subsequent differentiation. It is likely that problems in rhombomere formation are the underlying cause of congenital nervous system defects involving cranial nerves, ganglia, and peripheral structures derived from the cranial neural crest (the part of the neural crest that arises from the hindbrain).

The exact relationship between early patterns of rhombomere-specific gene transcription and subsequent cranial nerve development remains a puzzle. Nevertheless, the correspondence between these repeating units in the embryonic brain and similar iterated units in the development of the insect body (see Figure 21.5) suggests that differential expression of transcription factors in specific regions is essential for the normal development of many species. In a wide variety of animals, spatially and temporally distinct patterns of transcription factor expression coincide with spatially and temporally distinct patterns of differentiation, including the differentiation of the nervous system. The idea that the bulges and folds in the neural tube are segments defined by patterns of gene expression provides an attractive framework for understanding the molecular basis of pattern formation in the developing vertebrate brain.

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The patterned expression of Hox genes, as well as other developmentally regulated transcription factors (many with homology to other patterning genes that influence development in *Drosophila*) and signaling molecules, does not by itself determine the fate of a group of embryonic neural precursors. Instead, this aspect of regionally distinct transcription factor expression during early brain development contributes to a broader series of genetic and cellular processes that eventually produce fully differentiated brain regions with appropriate classes of neurons and glia.

Genetic Abnormalities and Altered Human Brain Development

The recent explosion of information about molecules that influence brain development provides a basis for reevaluating the causes of a number of congenital brain malformations, as well as various forms of mental retardation. For instance, some forms of **hydrocephalus** (caused by impeded flow of cerebrospinal fluid, which increases pressure and results in enlarged ventricles and eventually cortical atrophy as a result of compression) can be traced to mutations of genes on the X chromosome, especially those in the L1 cell adhesion molecule (see Chapter 22). Similarly, **fragile-X syndrome**, the most common form of congenital mental retardation, is associated with triplet repeats in a subset of genes on the X chromosome, particularly the fragile-X protein, which is involved in stabilizing dendritic processes and synapses.

Beyond these X-linked abnormalities, there are at least two genetic disorders that compromise the nervous system generated by single gene mutations in homeobox-like transcription factors. **Aniridia** (characterized by loss of the iris in the eye and mild mental retardation) and **Waardenburg syndrome** (characterized by craniofacial abnormalities, spina bifida, and hearing loss) are caused by mutations in the *Pax6* and *Pax3* genes, respectively, both of which produce transcription factors (see Box C). Finally, developmental disorders such as **autism** and other severe social or learning impairments have been linked in some cases to mutations in specific genes (including some of the Wnt family), as well as to microdeletions or duplications of specific chromosomal regions. Perhaps the best known example of this class of neurodevelopmental disorders is Down syndrome or **trisomy 21**, which is caused by the duplication of part or all of chromosome 21, usually due to failure of meiosis during the final stages of oogenesis. This duplication leads to three copies of the genes on chromosome 21; an as yet unknown subset of these genes leads to increased levels of the relevant proteins and altered neural development.

Although the connections between these aberrant genes and the resulting anomalies of brain development are not yet understood, such correlations provide a starting point for exploring the molecular pathogenesis of many congenital disorders of the nervous system.

The Initial Differentiation of Neurons and Glia

Once the neural tube has developed into a rudimentary brain and spinal cord, the generation and differentiation of the permanent cellular elements of the brain—neurons and glia—begins in earnest. As noted in Chapter 1, the mature human brain contains about 100 billion neurons and many more glial cells, all generated over the course of only a few months from a small population of precursor cells. Except for a few specialized cases (see Chapter 24), the entire neuronal complement of the adult brain is produced during a time window that closes before birth; thereafter, precursor cells disappear, and few if any new neurons can be added to replace those lost by age or injury in most brain regions. The precursor cells are located in the **ventricular zone**, the innermost cell layer surrounding the lumen of the neural tube, and a region of extraordinary mitotic activity. It has been estimated that in humans, about 250,000 new neurons are generated each minute during the peak of cell proliferation during gestation.

The dividing precursor cells in the ventricular zone undergo a stereotyped pattern of cell movements as they progress through the mitotic cycle, leading to the formation of either new stem cells or postmitotic neuroblasts that differentiate into neurons (Figure 21.7). As cells become postmitotic, they leave the ventricular zone and migrate to their final positions in the developing brain. Knowing when the neurons destined to populate a given brain region are "born"—that is, when they become postmitotic (determined by performing birthdating studies; Box E)—has given considerable insight into how different regions of the brain are constructed. Different populations of spinal cord neurons as well as nuclei of the brainstem and thalamus are distinguished by the times when their component neurons are generated, and some of these distinctions are influenced by local differences in signaling molecules and transcription factors that characterize the precursors (see Figure 21.9). In the cerebral cortex, most neurons of the six layers of the cortex are generated in an inside-out manner (see Box F for an intriguing exception to this rule). The firstborn cells are eventually located in the deepest layers, while later generations of neurons migrate radially from the site of their final division in the ventricular zone through the older cells and come to lie superficial to them (Figure 21.8). Indeed, in most regions of the brain where

Box E

Neurogenesis and Neuronal Birthdating

The process by which neurons are generated is generally referred to as neurogenesis. The time at which neurogenesis occurs for any particular neuron is called its neuronal "birthdate." At some point in development, stem cells—the dividing cells that populate the proliferative zones of the developing brain—undergo asymmetrical divisions that produce both another stem cell and a neuronal precursor (called a neuroblast) that will never again undergo cell division. Because neurons are generally unable to reenter the cell cycle once they have left it, the point at which a neuronal precursor leaves the cycle defines the birthdate of the resulting neuron.

In animals with extraordinarily simple nervous systems, such as the worm *Caenorhabditis elegans*, it is possible to directly monitor in a microscope each embryonic stem cell as it undergoes its characteristic series of cell divisions, and to thereby determine when a specific neuron is born. In the vastly more complex vertebrate brain, however, this approach is not feasible. Instead, neurobiologists rely on the characteristics of the cell cycle itself to label cells according to their date of birth. When cells are actively replicating DNA, they take up nucleotides—the building blocks of DNA (see Figure 21.6). Cell birthdating studies use a labeled nucleotide that can be incorporated only into newly synthesized DNA—usually tritium-labeled thymidine or a chemically distinctive analog of thymidine (the DNA-specific nucleotide) such as bromodeoxyuridine (BrDU)—at a known time in the organism's developmental history. All stem cells that are actively synthesizing DNA incorporate the labeled tag and pass it on to their descendants. Because the labeled probe is only available for minutes to hours after being injected, if a stem cell continues to divide, the levels of the labeled probe in the cell's DNA are quickly diluted. However, if a cell undergoes only a single division after incorporating the label and produces a postmitotic neuroblast, that neuron retains high levels of the labeled DNA indefinitely. Once the animal has matured, histological sections prepared from the brain show the labeled neurons. The most heavily labeled cells are those that incorporated the tag just before their final division; they are therefore said to have been "born" at the time of injection.

One of the earliest insights obtained from this approach was that the layers of the cerebral cortex develop in an "inside-out" fashion (see Figure 21.7). In certain mutant mice, such as *reeler* (see Box B in Chapter 18), birthdating studies show that the oldest cells end up erroneously in the most superficial layers and the most recently generated cells in the deepest as a result of defective migration. Although neuronal birthdates do not, in themselves, tell the lineage of cells, or when they acquire specific phenotypic or molecular features, they mark a major transition in the genetic programs that dictate when and how nerve cells differentiate.

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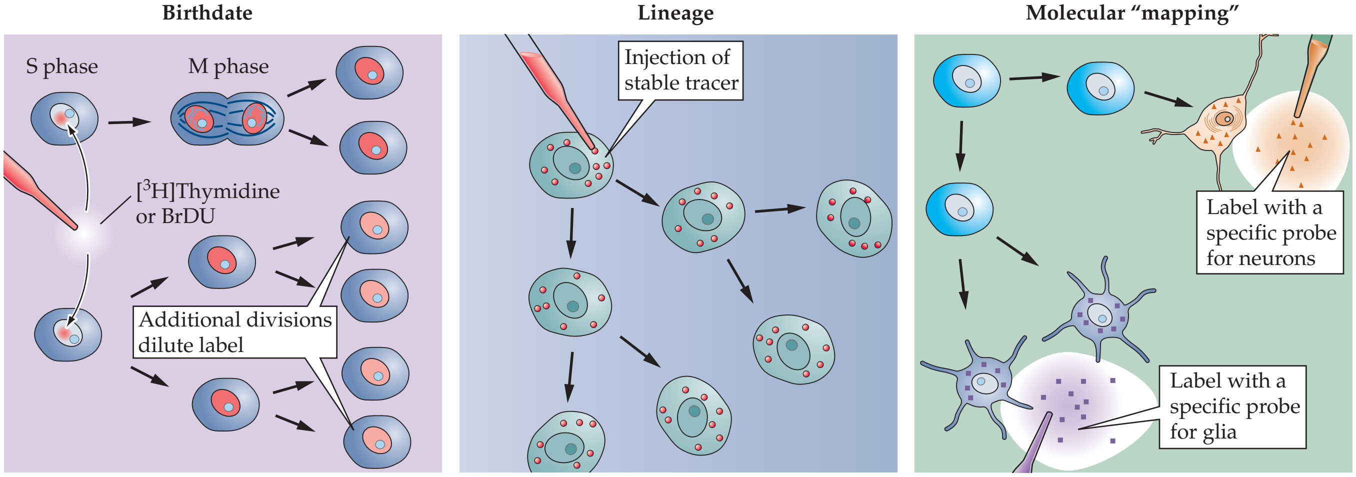
Birthdate
S phase
M phase
[^{3}H]Thymidine or BrDU
Additional divisions dilute label
Lineage
Injection of stable tracer
Molecular "mapping"
Label with a specific probe for neurons
Label with a specific probe for glia

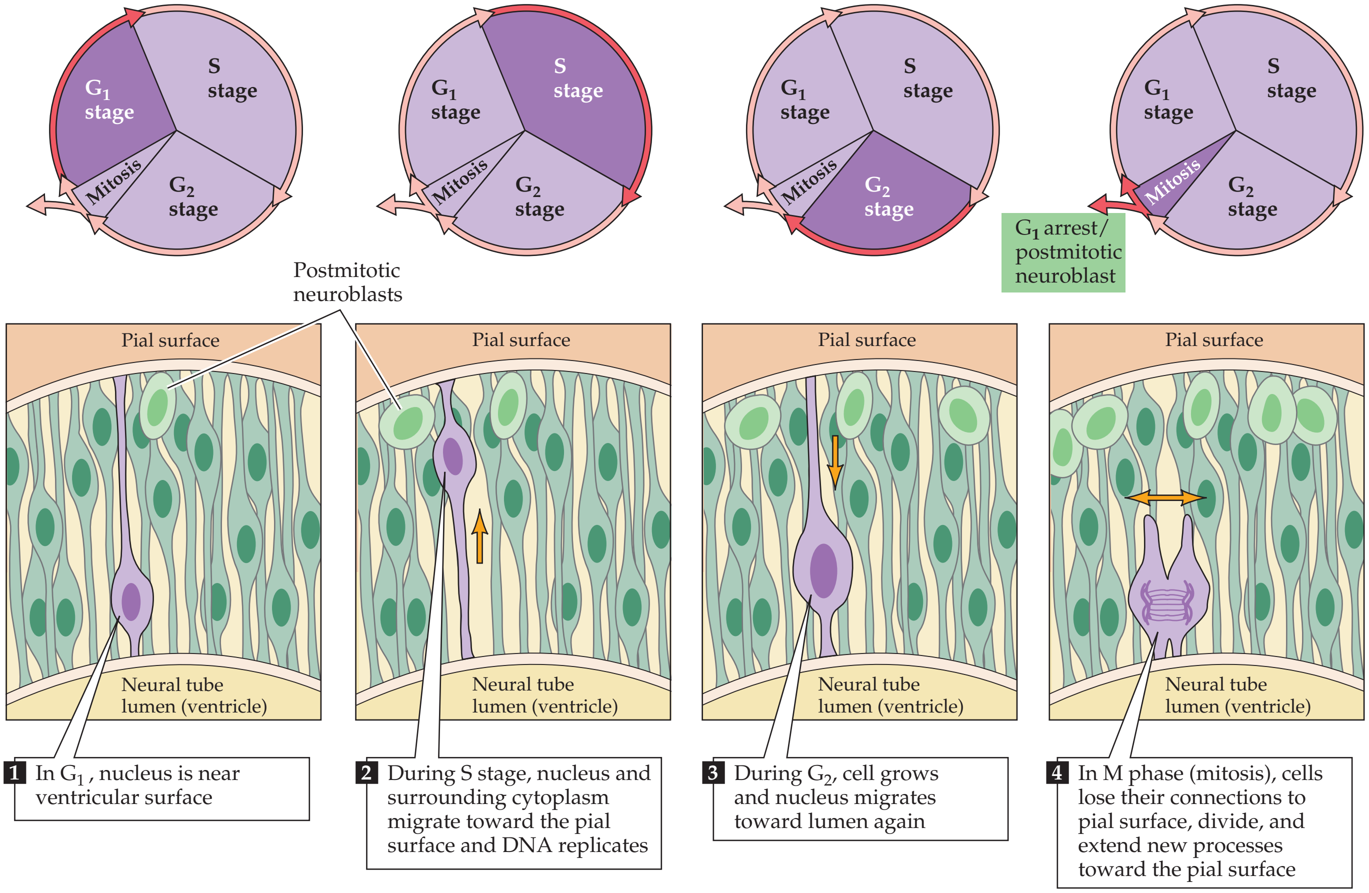
G_1 stage
S stage
Mitosis
G_2 stage
G_1 arrest/ postmitotic neuroblast
Postmitotic neuroblasts
Pial surface
Neural tube lumen (ventricle)
1 In G_1, nucleus is near ventricular surface
2 During S stage, nucleus and surrounding cytoplasm migrate toward the pial surface and DNA replicates
3 During G_2, cell grows and nucleus migrates toward lumen again
4 In M phase (mitosis), cells lose their connections to pial surface, divide, and extend new processes toward the pial surface

Figure 21.7 Dividing precursor cells in the vertebrate neuroepithelium (neural plate and neural tube stages) are attached both to the pial (outside) surface of the neural tube and to its ventricular (lumenal) surface. The nucleus of the cell translocates between these two limits within a narrow cylinder of cytoplasm. When cells are closest to the outer surface of the neural tube, they enter a phase of DNA synthesis (the S stage); after the nucleus moves back to the ventricular surface (the G_2 stage), the precursor cells lose their connection to the outer surface and enter mitosis (the M stage). When mitosis is complete, the two daughter cells extend processes back to the outer surface of the neural tube, and the new precursor cells enter a resting (G_1) phase of the cell cycle. At some point a precursor cell generates either another stem cell that will go on dividing and a daughter cell—a neuroblast—that will not divide further, or two postmitotic daughter cells.

neurons are arranged into layered structures (hippocampus, cerebellum, superior colliculus) there is a systematic relationship between the layers and the time of cell origin. Thus, each layer consists of a cohort of cells generated during a specific developmental period. The implication of this phenomenon is that common periods of neurogenesis are important for the development of the cell types and connections that characterize each layer.

The Generation of Neuronal Diversity

The neuronal precursor cells in the ventricular zone of the embryonic brain look and act more or less the same. Yet these precursors ultimately give rise to postmitotic cells that are enormously diverse in form and function. The spinal cord, cerebellum, cerebral cortex, and subcortical nuclei (including the basal ganglia and thalamus) each contain several neuronal cell types distinguished by morphology, neurotransmitter content, cell surface molecules, and the types of synapses they make and receive. On an even more basic level, the stem cells of the ventricular zone produce both neurons and glia—cells with markedly different properties and functions. How and when are these different cell types determined?

The bulk of the evidence favors the view that neuronal differentiation is based primarily on local cell–cell interactions followed by distinct histories of transcriptional regulation via a "code" of transcription factors expressed in each cell (Figure 21.9). Historically, most experimental approaches to this issue have relied on transplantation strategies, such as moving bits of a par-

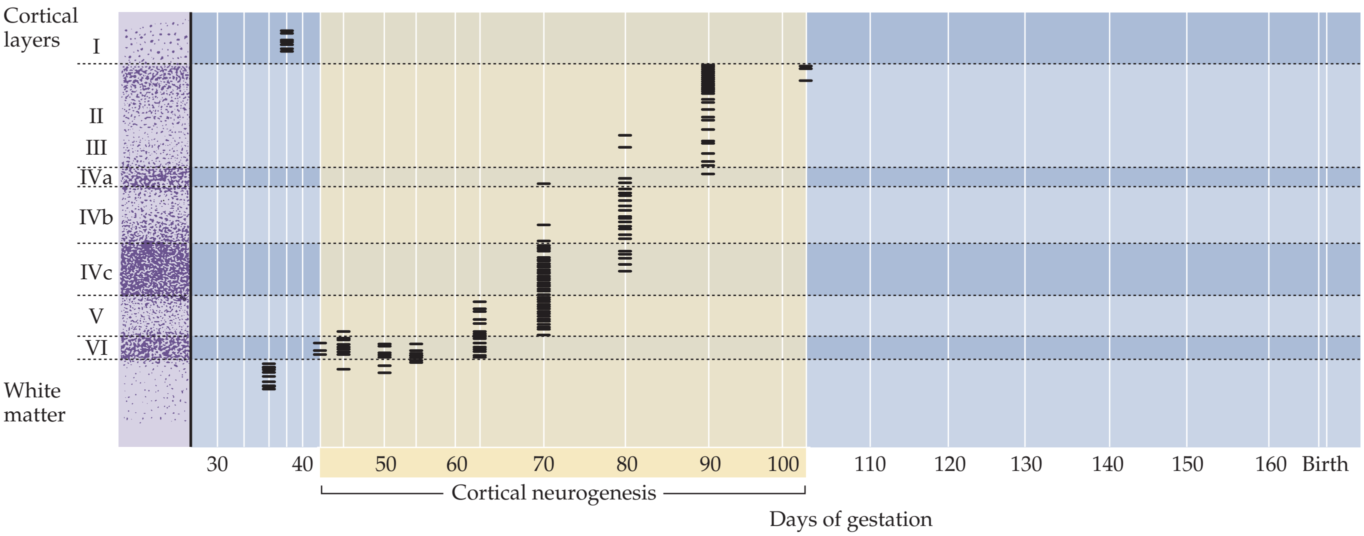

Figure 21.8 Generation of cortical neurons during the gestation of a rhesus monkey (a span of about 165 days). The final cell divisions of the neuronal precursors, determined by maximal incorporation of radioactive thymidine administered to the pregnant mother (see Box E), occur primarily during the first half of pregnancy and are complete on or about embryonic day 105. Each short horizontal line represents the position of a neuron heavily labeled by maternal injection of radiolabeled thymidine at the time indicated by the corresponding vertical line. The numerals on the left designate the cortical layers. The earliest generated cells are found in a transient layer called the subplate (a few of these cells survive in the white matter) and in layer I (the Cajal-Retzius cells). (After Rakic, 1974.)

ticular brain region to a different location in the brain of a host animal to determine whether the transplanted cells acquire the host phenotype or retain their original fate during subsequent development. In general, when very young precursor cells are transplanted, they tend to acquire the host phenotype. Transplanted cells at increasingly older ages, however, usually retain the original phenotype.

The use of genetic approaches, particularly in simple, so-called “model” organisms such as fruit flies and the worm *Caenorhabditis elegans*, has made clear the essential role of local cell–cell interactions, and has indicated some of the molecules that mediate these processes in neural fate determination. In the fruit fly eye, the position and identity of a variety of photoreceptor cells with distinct visual functions relies upon signaling mediated by cell surface ligands on one class of cells and specific receptor kinases on adjacent cells (Figure 21.10). In *C. elegans*, the determination of midline neurons reflects their lineage, the proper functioning of genes involved in cell–cell signaling, and whether subsets of precursors survive or die during programmed cell death, or **apoptosis**.

Similar local interactions have been invoked to explain differentiation of a number of neuronal and glial classes in the developing vertebrate brain. Perhaps not surprisingly, many of the signaling molecules that are essential for initial steps of neural induction and regionalization—retinoic acid, the FGFs, BMPs, shh, and Wnts—all influence the genesis of specific classes of neurons and glia via local cell–cell interactions (see Figure 21.9). Some of the additional signaling molecules that contribute to these processes in the vertebrate brain include the **notch** family of cell surface ligands and their receptors, the **delta** family which tend to maintain precursors in a less differentiated state. Among the targets of these signals, a subset of transcription factor genes known as the **bHLH genes** (named for a shared basic *h*elix-*l*oop-*h*elix amino acid motif that defines the DNA binding domain) has emerged as central to subsequent differentiation of distinct neural or glial fates.

These molecular details provide an outline of how general cell classes are established; however, there is presently no clear and complete explanation for how any specific neuronal class achieves its identity. This gap in knowledge presents a problem in using neural stem cells to generate replacements for specific cell classes lost in neurodegenerative diseases or after brain injury (see Box A).

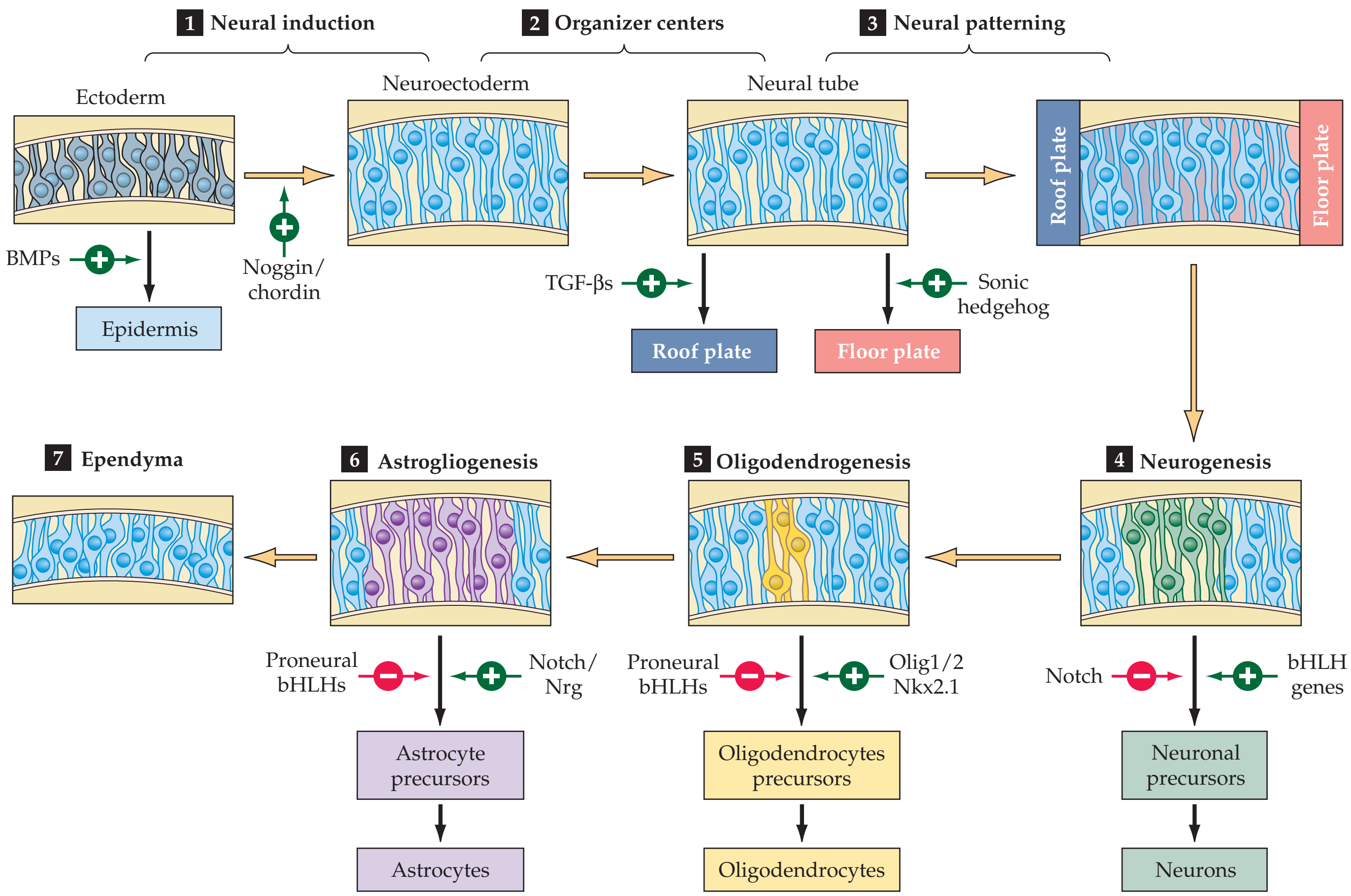
1 Neural induction
2 Organizer centers
3 Neural patterning
Ectoderm
Neuroectoderm
Neural tube
Roof plate
Floor plate
BMPs
Epidermis
Noggin/ chordin
TGF-βs
Roof plate
Sonic hedgehog
Floor plate
7 Ependyma
6 Astrogliogenesis
5 Oligodendrogenesis
4 Neurogenesis
Proneural bHLHs
Notch/ Nrg
Astrocyte precursors
Astrocytes
Proneural bHLHs
Olig1/2 Nkx2.1
Oligodendrocytes precursors
Oligodendrocytes
Notch
bHLH genes
Neuronal precursors
Neurons

Figure 21.9 Essential molecular and cellular mechanisms that guide neuronal and glial differentiation in the neural ectoderm. (1–3) The steps by which ectoderm acquires its identity as neural ectoderm. Generation of neural precursors, or stem cells, relies first on the balance of BMP and its endogenous antagonists like noggin and chordin in the developing embryo. Next, local sources of inductive signals, including TFG-β family members and sonic hedgehog, establish gradients that influence subsequent neural precursor identities, as well as identifying local "organizers" (such as the floorplate and roofplate) that define the cellular identity of the inductive signaling centers. (4–7) Steps thought to define neurons, oligodendroglia, and astrocytes from multipotent neuronal precursors. Balanced signaling activity of notch and transcriptional control of the bHLH proneural genes (named based on their ability to bias neural progenitor cells toward a differentiate neural fate) influence neurogenesis. Similarly, antagonistic transcriptional regulation via either the bHLH genes or three additional transcription factors, Olig1, Olig2, and Nkx2.2, influence the generation of oligodendroglia. Continued antagonism between bHLH genes, notch signaling, and the signal molecule neureglin (Nrg) is thought to influence the generation of mature astrocytes. Finally, in the adult brain, cells adjacent to the ventricles (which apparently have avoided becoming differentiated) remain as ependymal cells. These may included a subpopulation of neural stem cells (see Box A). (After Kintner, 2002.)

Neuronal Migration

The cellular positioning that constrains local signaling depends on **migration** of postmitotic neuroblasts in the fetal brain. Migration is a ubiquitous feature of development that brings cells into appropriate spatial relationships. In the nervous system, migration during development brings different classes of neurons together so that they can interact appropriately. The final location of a postmitotic nerve cell is presumably especially critical, since neural function depends on precise connections made by neurons and their targets. In short, the developing presynaptic and postsynaptic elements must be in the right place at the right time.

After their final mitosis in the ventricular zone, most neuroblasts migrate substantial distances. For neurons of the central nervous system, this migration remains within the limits of the neural tube. However, neurons of the peripheral nervous system, which come from the neural crest, arise from cells that have often journeyed a considerable distance through several embryonic environments (see Figure 21.2). Even within the central nervous system, the significant distances traversed are obvious in large animals like primates. To form the cerebral cortex, for example, neurons must sometimes travel several millimeters from the ventricular zone to the pial surface.

A good deal is now known about the mechanics of how neurons move from their birthplace to their final destina-

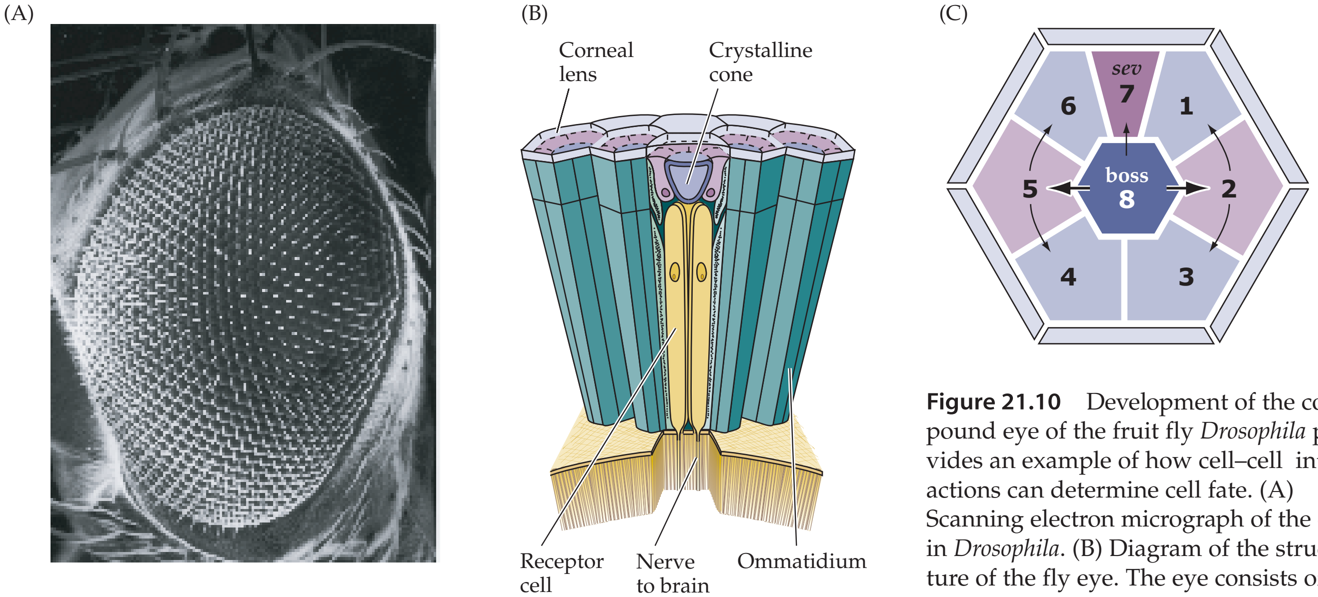

Figure 21.10 Development of the compound eye of the fruit fly *Drosophila* provides an example of how cell–cell interactions can determine cell fate. (A) Scanning electron micrograph of the eye in *Drosophila*. (B) Diagram of the structure of the fly eye. The eye consists of an array of identical ommatidia, each comprising an array of eight photoreceptors. (C) Arrangement of photoreceptors within each ommatidium and the cell–cell signaling that determines their fate. A membrane-bound ligand on R8 (the *boss* gene product) binds to a receptor (encoded by the *sevenless* gene, *sev*) on the R7 cell. These interactions eventually lead to the changes in gene expression that determine the fate of an R7 cell. The arrows between R8 and the remaining receptor cells indicate interactions necessary for determining the fates of R1–R6. (A courtesy of T. Venkatesh; B,C after Rubin, 1989.)

tion. Depending on the area of the developing nervous system in which they originate, migrating neurons follow one of two strategies. Neural crest cells are largely guided along distinct migratory pathways by specialized adhesion molecules in the extracellular matrix or by molecules on the surfaces of cells in the embryonic periphery (see Figure 21.2). At different developmental stages, similar molecules are probably used to guide axonal outgrowth (see Chapter 22). In contrast, neurons in many regions, including the cerebral cortex, cerebellum, hippocampus, and spinal cord, are guided to their final destinations by crawling along a particular type of glial cell, called **radial glia**, which act as cellular guides (Figure 21.11).

Histological observations of embryonic brains made by Wilhelm His and Ramon y Cajál during the nineteenth and early twentieth centuries suggested that neuroblasts crawled along glial guides to their final locations (Figure 21.11A). These observations were supported by analyses of electron microscopic images of fixed tissue in the 1960s and 1970s (Figure 21.11B,C), which fit well with the orderly relationship between birthdates and final position of distinct cell types in the cerebellum and cerebral cortex (see Figure 21.7 and Box E). Subsequently, innovations in cell culture techniques and light microscopy made it possible to observe the process of migration directly. When radial glial cells and immature neurons are isolated from the developing cerebellum or cerebral cortex and mixed together in vitro, the neurons attach to the glial cells, assume the characteristic shape of migrating cells seen in vivo, and begin moving along the glial processes. Indeed, the membrane constituents of glial cells, when coated onto thin glass fibers, support this sort of normal migration. Several cell surface adhesion molecules, extracellular matrix adhesion molecules, and associated signal transduction molecules apparently mediate this process. Many of these molecules are also essential for subsequent steps in neural development, such as axon growth and guidance (see Chapter 22). Although in many regions of the brain—particularly those that give rise to nuclear cell groups—neurons migrate without the benefit of glial guides (Box F) migration along radial glial fibers is always seen in regions where cells are organized into layers, such as the cerebral cortex, hippocampus, and cerebellum. Both neuropathological

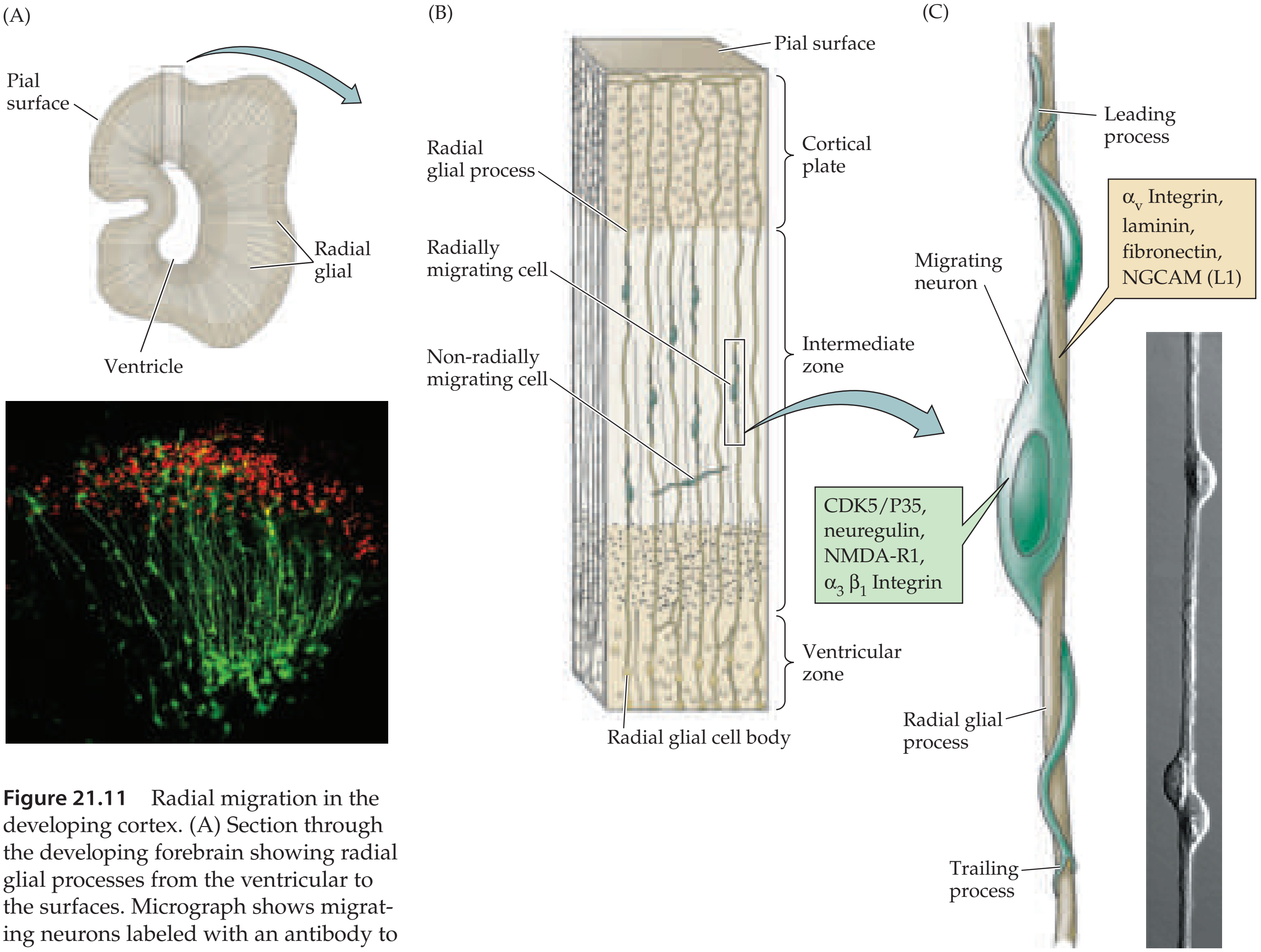
(A)
Pial surface
Radial glial
Ventricle
(B)
Pial surface
Radial glial process
Cortical plate
Radially migrating cell
Intermediate zone
Non-radially migrating cell
Ventricular zone
Radial glial cell body
(C)
Leading process
α_v Integrin, laminin, fibronectin, NGCAM (L1)
Migrating neuron
CDK5/P35, neuregulin, NMDA-R1, α_3 β_1 Integrin
Radial glial process
Trailing process

Figure 21.11 Radial migration in the developing cortex. (A) Section through the developing forebrain showing radial glial processes from the ventricular to the surfaces. Micrograph shows migrating neurons labeled with an antibody to neuregulin, specific for migrating cortical neurons. (B) Enlargement of boxed area in (A). Migrating neurons are intimately apposed to radial glial cells, which guide them to their final position in the cortex. Some cells take a nonradial migratory route, which can lead to wide dispersion of neurons derived from the same precursor (see Box F). (C) A single neuroblast migrates upon a radial glial process (based on serial reconstruction of EM sections as well as in vitro assays of migration, as shown in the accompanying micrograph). Cell adhesion and other signaling molecules or receptors found on the surface of either the neuron (green) or the radial glial process (tan) are indidated in the respective boxes. (After Rakic, 1974; micrographs courtesy of E. S. Anton and P. Rakic.)

observations and more recent molecular and genetic studies indicate that some forms of mental retardation, epilepsy, and other neurological problems arise from the abnormal migration of cerebral cortical neurons (see Box B in Chapter 18).

Relatively little is known about the specific messages that neurons receive as they migrate in the central nervous system. It is apparent, however, that moving through a changing cellular environment has important consequence for the differentiation of neurons. Such effects are most thoroughly documented in the migration of neural crest cells, where the migratory paths of precursor cells are related to both the ultimate position in the body and neuronal identity. The distinct signals along these pathways can be secreted molecules (including some of the peptide hormones used at earlier times for neural induction), cell surface ligands and receptors (adhesion molecules and other signals), or extracellular matrix molecules (see Chapter 22). These signals are made available from somites, visceral epithelial structures like the developing dorsal aorta, mesodermally derived mesenchymal cells, and the neural crest cells themselves.

Of particular significance is the fact that specific peptide hormone growth factors cause neural crest cells to differentiate into distinct phenotypes (Figure 21.12). These effects depend on the location of the neuronal precursor cell along a migratory pathway, different signals being available at different points. Such position-dependent cues are probably not restricted to the peripheral nervous system; in the cerebellum, for example, different patterns of genes are expressed in migrating granule neurons at different locations, implying the existence of different signals (as yet unknown) along the migratory path.

Thus, neuronal migration involves much more than the mechanics of moving cells from one place to another. As in the case of inductive events during the initial formation of the nervous system, stereotyped movements bring different classes of cells into contact with one another, thereby providing a means of constraining cell–cell signaling to specific times and places.

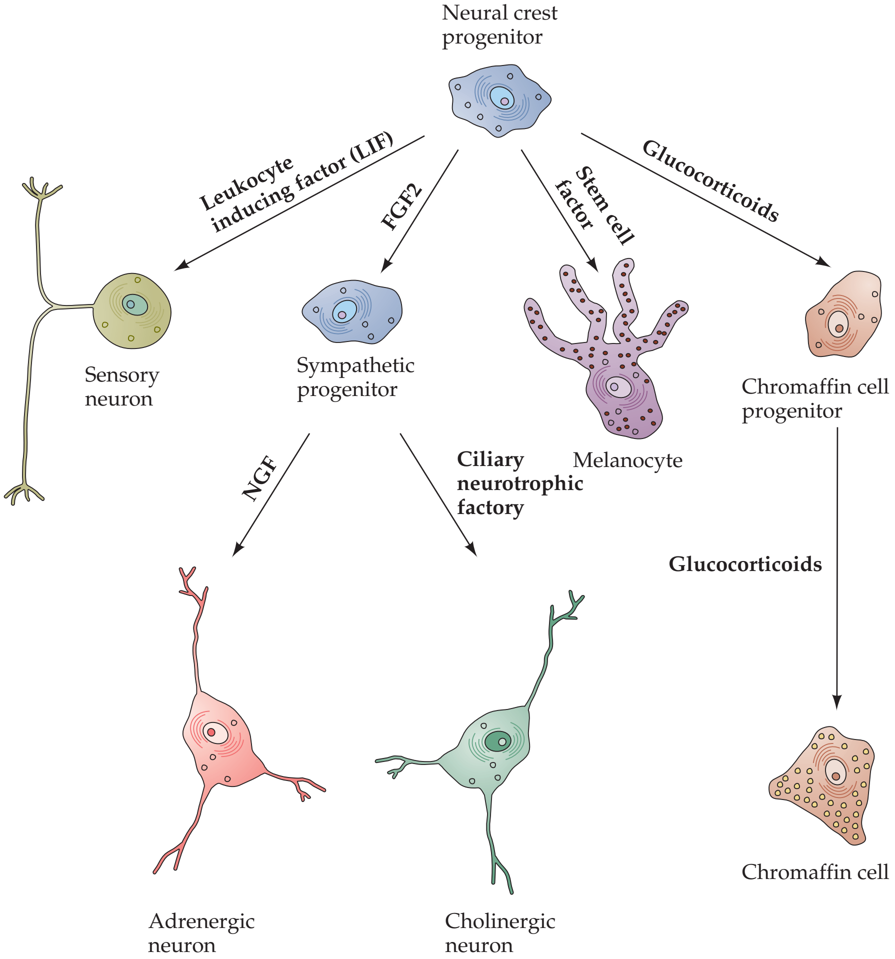
Neural crest progenitor
Leukocyte inducing factor (LIF)
FGF2
Stem cell factor
Glucocorticoids
Sensory neuron
Sympathetic progenitor
Melanocyte
Chromaffin cell progenitor
NGF
Ciliary neurotrophic factory
Glucocorticoids
Adrenergic neuron
Cholinergic neuron
Chromaffin cell

Figure 21.12 Cell signaling during the migration of neural crest cells. The establishment of each precursor type relies on signals provided by one of several specific peptide hormones. The availability of each signal depends on the migratory pathway.

Box F

Mixing It Up: Long-Distance Neuronal Migration

For many years, developmental neurobiologists assumed that position was destiny in the developing brain. For example, if a neuron was found in the thalamus, cerebellum, or cerebral cortex in the adult brain, it most likely came from a neural progenitor cell in the embryonic brain region that gave rise to the thalamus, cerebellum, or cerebral cortex. The identification of rhombomeres and subsequent evidence that these domains are compartments between which little mixing of cells occurs reinforced this notion. Nevertheless, a few observations hinted that all neurogenesis might not be local, and eventually led to a new idea of how neuronal classes in a variety of brain regions are integrated into mature structures and circuits.

The initial indication of this tendency for subsets of neurons to wander came in the late 1960s with a report that neurons in the pulvinar, a thalamic nucleus assumed to be derived from the diencephalon, were actually generated in the telencephalon. This observation received little notice until the mid 1980s, when a series of experiments using chick–quail chimeras suggested that a major portion of granule cells in the cerebellum (small local circuit neurons) were actually generated outside the rhombencephalon (the embryonic region associated with the generation of the cerebellum). Most of these extrinsic cells were thought to migrate from the mesencephalon (associated with the generation of the superior and inferior colliculus in the adult brain) into the external granule cell layer of the cerebellum. Together, these findings implied that adult brain structures might be derived from a broad range of embryonic brain subdivisions.

Around the same time, several investigators noticed a small but consistent proportion of cells in the cerebral cortex whose migratory route was apparently tangential rather than radial (via radial glial guides). These observations were the focus of a lively debate that nevertheless failed to explain the significance of the apparent "escapees" from the radial migration framework in the developing cortex. Moreover, lineage analysis suggested that cortical projection neurons, interneurons, astrocytes and oligodendroglia were probably not derived from the same precursor pools. There was little consensus about these disparate observations until the mid 1990s when several groups realized that there was a massive migration of cells from the ventral forebrain—the region of the ganglionic eminence that gives rise to the caudate, putamen, and globus pallidus—to the cerebral cortex (Figure A). Moreover, these ventrally derived cells were not just any cell types; they constituted distinct classes of GABAergic interneurons in the cortex and olfactory bulb, as well as oligodendroglia throughout the entire forebrain. Newly generated granule and periglomular interneurons in the mature olfactory bulb are derived from a remnant of the ganglionic eminence called the anterior subventricular zone, which persists at the surface of the mature lateral ventricles.

A mosaic of transcriptional regulators whose expression and activity is restricted to various domains in the ventral forebrain orchestrates this long distance migration of distinct cell types (Figure B). When subsets of these transcription factors are mutated, migration of cells from the ventral forebrain to the cortex is dramatically diminished (Figure C), and the numbers of GABAergic interneurons is similarly reduced. The mechanisms for specifying cell identity, migration and destination remain unknown; nevertheless, this regional diversity is apparently a consistent feature of neurogenesis in mammalian brains. Nevertheless, not all neurons participate in this long-distance migration. In the human brain, for example, some GABAergic interneurons are generated locally in the cortical rudiment, in addition to those that migrate from the ventral forebrain. These locally generated interneurons apparently use the same radial glial migratory route as their glutamatergic neighbors.

The developmental and functional significance of this mixing of offspring from progenitors in various embryonic brain regions remains unknown. Perhaps the range and number of cell–cell interactions necessary to generate functionally distinct cell types is so large that the appropriate population can only be determined by exposing subsets of cells to a variety of environments, and then having those cells act as messengers to deliver additional molecular signals at a new location. Regardless of the purpose of this arduous journey, its consequence is the orderly establishment of cellular diversity in a number of brain regions.

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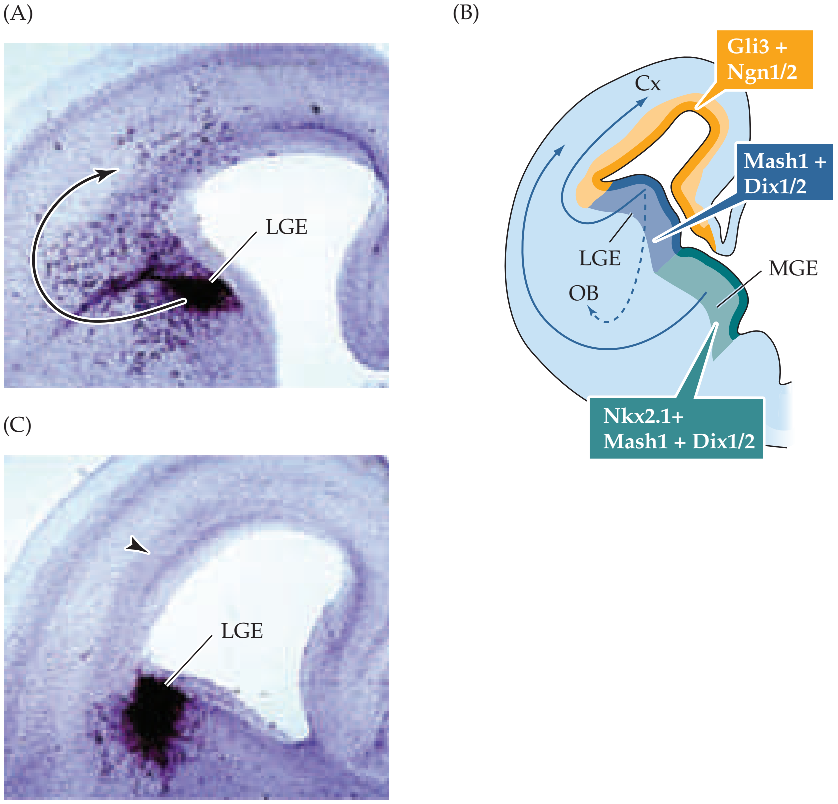

(A) Migration of cells from the ventral forebrain to the neocortex during late gestation in the mouse. A tracer has been placed in the lateral ganglionic eminence, and labeled cells can be seen streaming toward the cortex, as well as in residence in the developing cortical plate. (B) Schematic of transcriptional regulators associated with the primary divisions of the ganglionic eminence (lateral and medial), and the basic migratory routes taken by cells in each division (arrows). (C) Diminished migration of cells from the ventral forebrain in mice with null mutations of both *Dlx1* and *Dlx2* (expressed throughout the lateral and medial ganglionic eminence).

Summary

The initial development of the nervous system depends on an intricate interplay of cellular movements and inductive signals. In addition to an early establishment of regional identity and cellular position as a result of morphogenesis, substantial migration of neuronal precursors is necessary for the subsequent differentiation of distinct classes of neurons, as well as for the eventual formation of specialized patterns of synaptic connections (see Chapter 22). The fate of individual precursor cells is not determined simply by their mitotic history; rather, the information required for differentiation arises largely from interactions between the developing cells and the subsequent activity of distinct transcriptional regulators. All of these events are dependent on the same categories of molecular and cellular phenomena: cell–cell signaling, changes in motility and adhesion, transcriptional regulation, and, ultimately, cell-specific changes in gene expression. The molecules that participate in signaling during early brain development are the same as the signals used by mature cells: hormones, transcription factors, other second messengers (see Chapter 7), as well as cell adhesion molecules. As might be expected, the identification and characterization of these molecules in the developing brain has begun to explain a variety of congenital neurological defects. Signaling and regulation of gene expression during early neural development are especially vulnerable to the effects of genetic mutations, and to the actions of the many drugs and toxins that can compromise the elaboration of a normal nervous system.

Additional Reading

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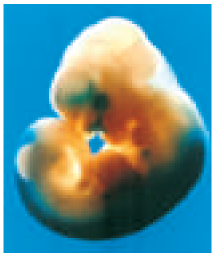
Chapter 22



Construction of Neural Circuits

Overview

Two central features of neural circuits must be established after neurons are generated and have migrated to their final positions. First, nerve cells in different regions must be linked together via axon pathways. Second, orderly synaptic connections must be made among appropriate pre- and postsynaptic partners. The cellular mechanisms that generate axon outgrowth and synapse formation are thus the major determinants of neural circuits that will eventually control behavior. The directed growth of axons and the recognition of synaptic targets is mediated by a specialization at the tip of each growing axon called the growth cone. Growth cones detect and respond to signaling molecules that identify correct pathways, prohibit incorrect trajectories, and ultimately facilitate functional synaptic partnerships. These include cell surface adhesion molecules and diffusible signals that either attract or repel growing axons. In addition, secreted growth factors influence axon growth and synapse formation as well as regulating appropriate numbers of connections between axons and their targets. As in other instances of intercellular communication, a variety of receptors and second messenger molecules transduce the signals provided to the growth cone. Thus cell–cell signals initiate intracellular events that underlie directed growth of the axon, the conversion of the growth cone into a presynaptic specialization, and the elaboration of a distinct postsynaptic site. The end results of the dynamic processes are a wealth of well-defined peripheral and central axon pathways and complex neural circuits that allow animals to behave in ever more sophisticated ways as they mature.

The Axonal Growth Cone

Among the many extraordinary features of nervous system development, one of the most fascinating is the ability of growing axons to navigate over millimeters or even centimeters, through complex embryonic terrain, to find appropriate synaptic partners. In 1910, Ross G. Harrison, who first observed axons extending in a living tadpole in vitro, noted that "The growing fibers are clearly endowed with considerable energy and have the power to make their way through the solid or semi-solid protoplasm of the cells of the neural tube. But we are at present in the dark with regard to the conditions which guide them to specific points."

Harrison's observations indicate the central features of axonal growth. First, the energy and power of growing axons reflect the cellular properties of the **growth cone**, a specialized structure at the tip of the extending axon. Growth cones are highly motile structures that explore the extracellular environment, determine the direction of growth, and then guide the extension of the axon in that direction. The primary morphological characteristic of a growth cone is a sheetlike expansion of the growing axon at its tip called a **lamellapodium**. When examined in vitro, numerous fine processes called **filopodia** rapidly form and disappear from the terminal expansion, like fingers reaching out to sense the environment (Figure 22.1). The cellular mechanisms that underlie these complex searching movements have become a focus of cell biological studies of axon growth and guidance. This aspect of growth cone mobility reflects rapid, controlled rearrangement of cytoskeletal elements—particularly molecules related to the **actin cytoskeleton**—which modulate changes in growth cone shape, and ultimately the course of the axon through developing tissues. These rearrangements are regulated by signals transduced from the environment through receptors and channels on the growth cone extracellular surface (see below, and Figure 22.2). The growth cone, therefore, can use actin-based and other cytoskeletally mediated mechanisms to generate force, cause filopodial extension, and thus promote further exploration of the local environment.

Santiago Ramón y Cajal, Harrison's contemporary, noted further that when growth cones move along an established pathway pioneered by other axons, they tend to be simple in shape (see Figure 22.3B). In contrast, when a growing axon first extends in a new direction or reaches a region where a choice must be made about the direction to take, the structure (and presumably motility) of its growth cone undergoes dramatic changes. The growth cone flattens and extends numerous filopodia, much as it does in a culture dish, suggesting an active search for appropriate cues to direct subsequent growth. These changes of growth cone shape at "decision points" have been observed in both the peripheral and central nervous system. In the periphery, the growth cones of motor neurons undergo shape changes as they enter the primordia of muscles in immature limbs, presumably facilitating the selection of appropriate targets in the developing musculature. In the central nervous system, growth cones in developing spinal cord, olfactory and optic nerves also change shape when they reach critical points in their trajectories. An example of the functional significance of growth cone exploration is the decision made by subsets of retinal axons at the optic chiasm where the partial crossing or decussation of retinal axons is important for establishing the circuitry for binocular vision. The growth cones of retinal axons slow down and acquire a complex shape as they "choose" whether or not to cross the midline. Perhaps not surprisingly, this growth cone behavior reflects a combination of local molecular cues at the developing optic chiasm as well as the identity of retinal ganglion cells based upon position in the retina (Box A).

Non-Diffusible Signals for Axon Guidance

The complex behavior of growth cones during axonal extension suggests the presence of specific cues that cause the growth cone to move in a particular direction. In addition, the growth cone itself must have a specialized array of receptors and transduction mechanisms to respond to these cues. The cues themselves—the "condition(s) which guide … growth cones" referred to by Harrison—remained elusive for more than half a century after his initial observations of axon growth. The identity of some of the relevant molecules has been established over the last 30 years. These signals comprise a large group of molecules associated with **cell adhesion** and cell-cell recognition throughout the organism, as well as with directed axon or growth cone motility in the developing nervous system. The association of specific cell

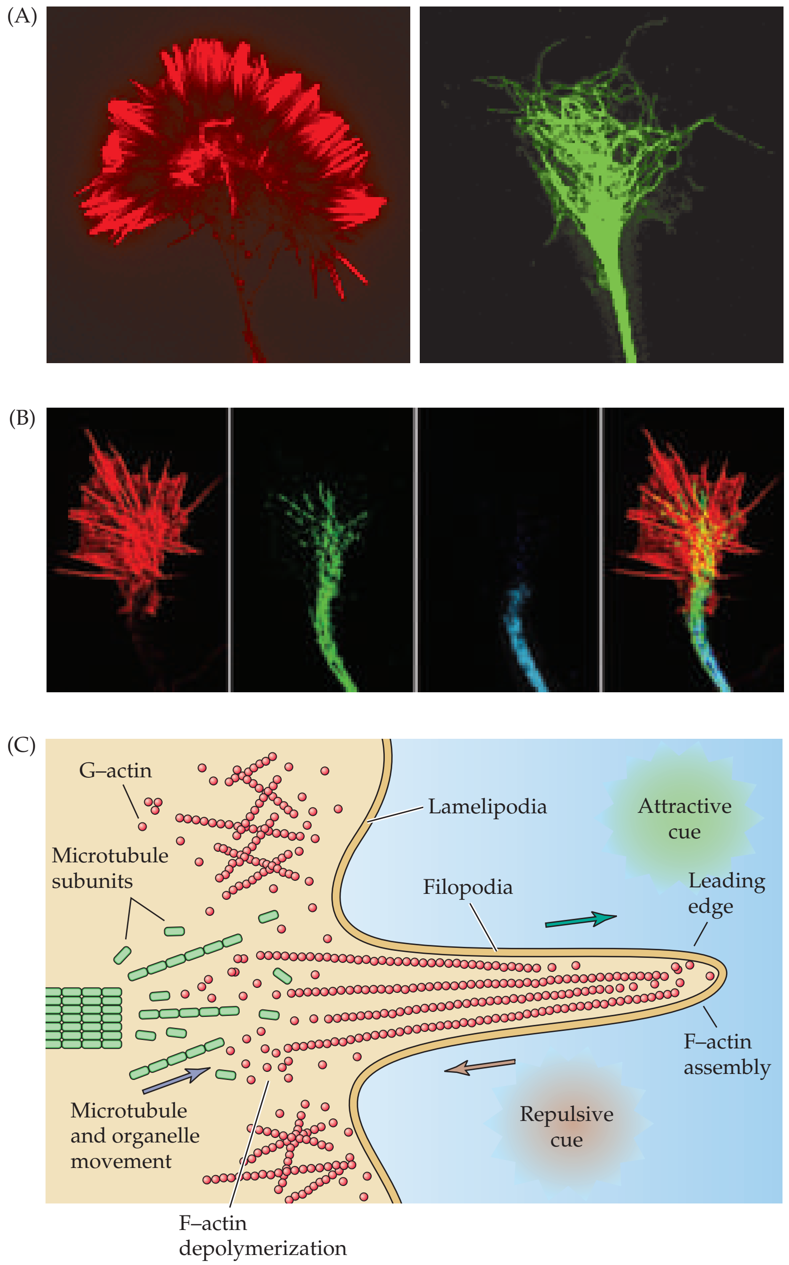

(A)
(B)
(C)
G–actin
Microtubule subunits
Lamelipodia
Attractive cue
Filopodia
Leading edge
F–actin assembly
Repulsive cue
Microtubule and organelle movement
F–actin depolymerization

Figure 22.1 Basic structure of the growth cone. (A) A growth cone from a cultured sensory ganglion neuron, labeled for actin (red) and tubulin (green). Actin predominates in the filopodial extensions of the growth cone. Tubulin is the predominant cytoskeletal protein in the axon, extending into the lamellapodium of the growth cone. (B) Distinct classes of actin and tubulin are seen in discrete regions. At left, filamentous actin (F-actin; red) is enriched in the growth cone lamellapodia. Tyrosinated microtubules are the primary constituents of the lamellar region of the growth cone (middle left; green). Actylated microtubules are restricted to the axonal region (middle right; blue). On the far right, a merged image shows the restricted distribution of each distinct cytoskeletal element. (C) Distribution and dynamics of cytoskeletal elements in the growth cone. Globular actin (G-actin) can be incorporated into F-actin at the leading edge of the filopodium in response to attractive cues. Repulsive cues support the disassembly and retrograde flow of G-actin toward the lamellapodium. Organized microtubules make up the cytoskeletal core of the axon, while more broadly dispersed, dynamic microtubules or microtubule subunits are found in apposition to F- and G-actin in the lamellapodium. (A courtesy of X. Zhou and W. Snider; B courtesy of E. Dent and F. Gertler; C after Kolodkin et al., 2003.)

Box A

Choosing Sides: Axon Guidance at the Optic Chiasm

The functional requirement that a subset of axons from retinal ganglion cells in each eye to cross while the remainder projects to the ipsilateral side of the brain was predicted based on optical principles—most notably by Issac Newton—and confirmed (much later) by neuroanatomists and neurophysiologists (see Chapter 11). The partial crossing, or decussation, of retinal axons is most striking in primates including humans, where approximately half of the axons cross and the other half do not. All other mammals have crossed and uncrossed retinal projections; however, the percentage of uncrossed axons diminishes from 20–30% in carnivores to less than 5% in most rodents. The frequency of uncrossed axons decreases even more in other vertebrates; thus in amphibians, fish, and birds most or all of the retinal projection is crossed. For both functional and evolutionary reasons, the partial decussation of the retinal pathways and its variable extent in different species has engaged the imagination of biologists and others interested in vision.

For developmental neurobiologists this phenomenon raises an obvious question: How do retinal ganglion cells choose sides so that some project contralaterally and others ipsilaterally? This question is central to understanding how the peripheral visual projection is organized to construct two accurate visual hemifield maps that superimpose points of space seen jointly by the two eyes (see Chapter 11). It also speaks to the more general issue in neural development of how axons distinguish ipsilateral and contralateral targets.

It is clear that the laterality of retinal axons is determined by initial cell identity and axon guidance mechanisms rather than by regressive processes that subsequently select or sculpt these projections. Thus, the distinction between the nasal and temporal retinal regions that project ipsilaterally and contralaterally is already apparent in the retina as well as in axon trajectories at the midline and in the developing optic tract, long before the axons reach their targets. In the retina, this specificity is seen as a "line of decussation," or border, between ipsilaterally and contralaterally projecting retinal ganglion cells, detected experimentally by injecting a retrograde tracer into the nascent optic tract of very young embryos. In the retinas of such embryos there is a distinct boundary between the population of retinal ganglion cells projecting ipsilaterally in one eye (found in the temporal retina), and a complementary boundary for contralaterally projecting cells in the other eye (see figure). A molecular basis for this specificity was initially suggested by studies of albino mammals, including mice and humans. In albinos, where single gene mutation disrupts melanin synthesis throughout the animal, including in the pigment epithelium of the retina, the ipsilateral component of the retinal projection from each eye is dramatically reduced, the line of decussation in the retina is disrupted, and the distribution of glia and other cells in the vicinity of the optic chiasm is altered. These and other observations suggested that identity of retinal axons with respect to decussation is established in the retina, and further reinforced by axonal "choices" influenced by cues provided by cells within the optic chiasm.

Cell biological analysis of growth cone morphologies showed that the chiasm is indeed a region where growth cones explore the molecular environment in a particularly detailed way, presumably to make choices pertinent to directed growth. Furthermore, molecular analysis showed that specialized neuroepithelial cells in and around the chiasm express a number of cell adhesion molecules associated with axon guidance. Interestingly, some of these molecules—particularly netrins, slits, and their robo receptors—do not influence decussation in the chiasm as they do at other regions of the nervous system. Instead, they are expressed in cells where the chiasm forms, apparently constraining its location on the ventral surface of the diencephalon. The establishment of ipsilateral versus contralateral identity is evidently more dependent on the zinc finger transcription factor *Zic2*, as well as cell adhesion molecules of the ephrin family. *Zic2*, which is expressed specifically in the temporal retina, is associated with the expression of a distinct Eph receptor, EphB1, in the axons arising from temporal retinal ganglion cells. The ephrin B2 ligand, which is recognized as a repellent of EphB1 axons, is found in midline glial cells in the optic chiasm. In support of the functional importance of these molecules, disrupting Zic2, EphB1 or ephrin B2 function diminishes the degree of ipsilateral projection in developing mice; in accord with this finding, neither *Zic2* nor ephrin B2 is expressed in vertebrate species that lack ipsilateral projections.

These observations thus provide a molecular framework for the identification of retinal ganglion cells and the sorting of their projections at the optic chiasm. How this sorting is related to the topopgraphy of tectal, thalamic, and cortical representations is not yet known. Most observations suggest that retinal topography is not faithfully preserved among axons in the optic tracts. The identity and position of axons from nasal and temporal retinas whose retinal ganglion cells "see" a common point in the binocular hemifield must therefore be restored in the thalamus, and subsequently retained or re-established in the thalamic projections to cortex. Choosing sides at the chiasm is only a first step in establishing maps of visual space.

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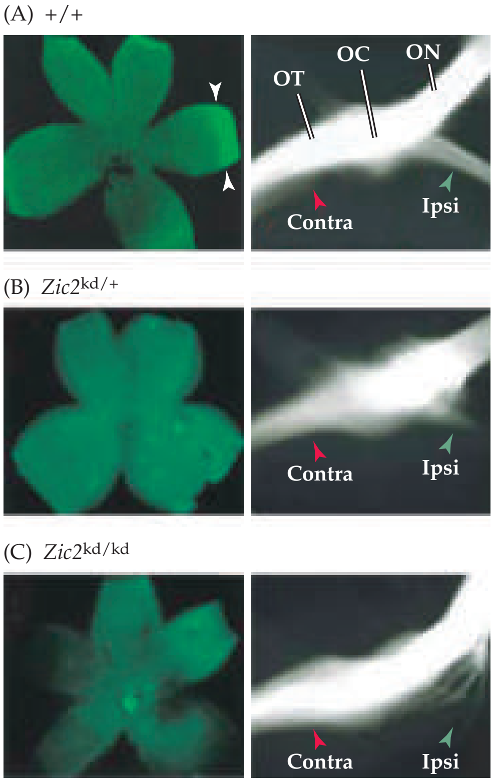


(A) There is a small population of Zic2-expressing retinal ganglion cells (arrowheads) in the ventrotemporal region of the normal retina (at left, mounted flat by making several radial cuts). At right, the normal projection of one eye via the optic nerve (ON), through the optic chiasm (OC), and into the optic tract (OT) has been traced using a lipophilic dye placed in one eye. After the chiasm, labeled axons can be seen both in the contralateral (contra) as well as the ipsilateral (ipsi) optic tract. (B) When *Zic2* function is diminished in a mouse heterozygous for a *Zic2* "knock-down" mutation (in which expression of Zic2 protein is diminished, but not eliminated, in the ventrotemporal retina), the number of ipsilateral axons in the optic tract is similarly diminished. (C) When Zic2 function is further diminished in homozygous *Zic2* knock-down animals, the ipsilateral projection can no longer be detected in the optic tract; thus, each of the optic tracts consist of contralateral axons. (From Herrera et al., 2003.)

adhesion molecules with axon growth is based upon experiments either in vitro, where addition or removal of a particular molecule results in modifying the relevant behavior of growing axons, or in vivo where genetic mutation, deletion or manipulation disrupts the growth, guidance or targeting of a particular axon projection (see Box A).

Despite their daunting number, molecules that are known to influence axon growth and guidance can be grouped into families of ligands and their receptors (Figure 22.2). The extracellular matrix molecules and their integrin receptors, the Ca^{2+}-independent cell adhesion molecules (CAMs), the Ca^{2+}-dependent cell adhesion molecules (cadherins), and the ephrins and eph receptors (see below) are the major classes of non-diffusible axon guidance molecules. The extracellular matrix cell adhesion molecules were the first to be associated with axon growth. The most prominent members of this group are the **laminins**, the **collagens**, and **fibronectin**. As their family name indicates, laminin, collagen, and fibronectin are all found in a macromolecular complex or matrix outside of the cell (Figure 22.3). The matrix components can be secreted by the cell itself or its neighbors; however, rather than diffusing away from the cell after secretion, these molecules form polymers and create a more durable local extracellular substance. A broad class of receptors, known collectively as **integrins**, bind specifically to these molecules (see Figure 22.2). Integrins themselves do not have kinase activity or other direct signaling capacity. Instead, the binding of laminin, collagen, or

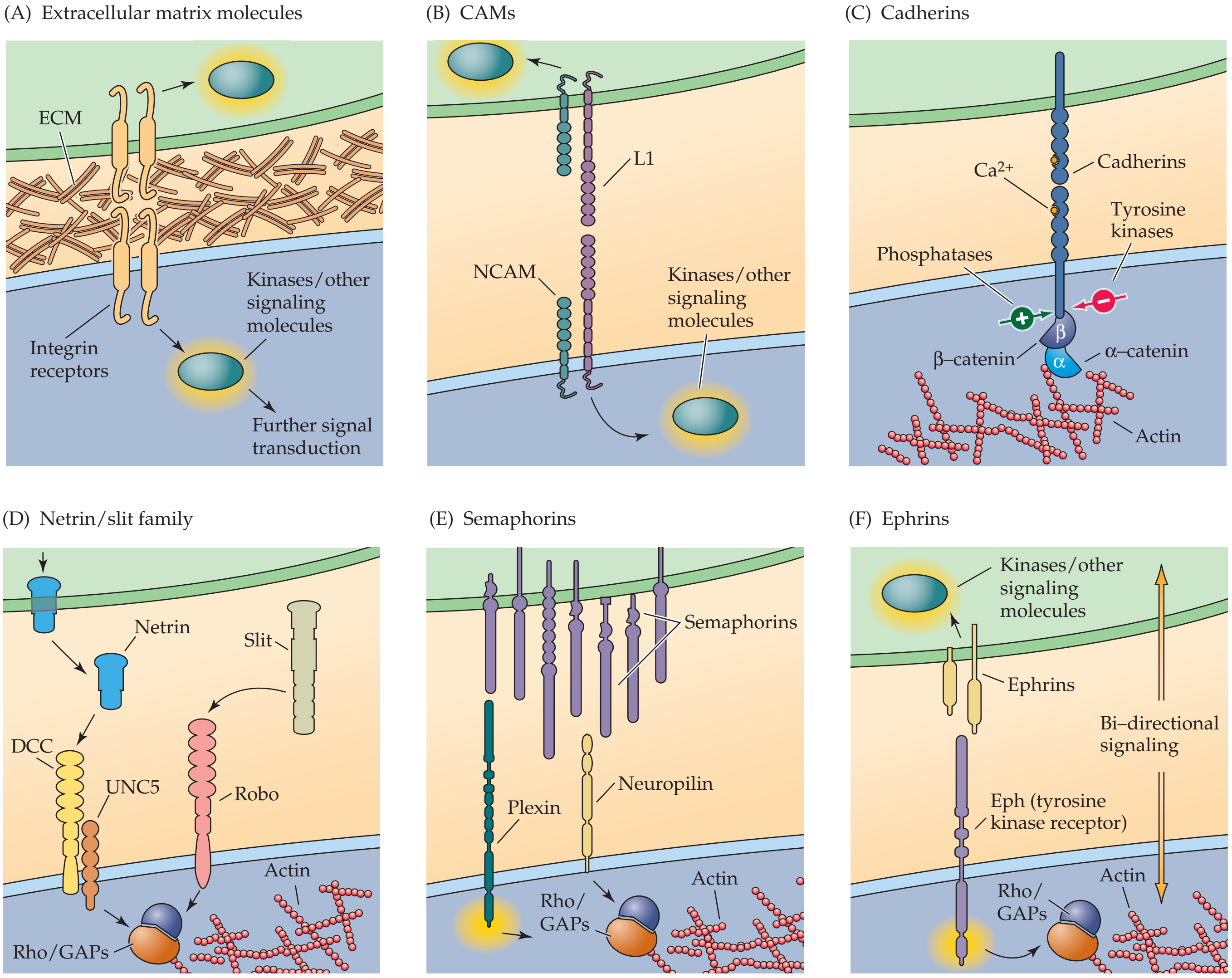

(A) Extracellular matrix molecules
ECM
Kinases/other signaling molecules
Integrin receptors
Further signal transduction
(B) CAMs
L1
NCAM
Kinases/other signaling molecules
(C) Cadherins
Ca2+
Cadherins
Tyrosine kinases
Phosphatases
β
β–catenin
α
α–catenin
Actin
(D) Netrin/slit family
Netrin
Slit
DCC
UNC5
Robo
Actin
Rho/GAPs
(E) Semaphorins
Semaphorins
Neuropilin
Plexin
Rho/ GAPs
Actin
(F) Ephrins
Kinases/other signaling molecules
Ephrins
Bi–directional signaling
Eph (tyrosine kinase receptor)
Rho/ GAPs
Actin

Figure 22.2 Several families of ligands and receptors constitute the major classes of axon guidance molecules. These ligand–receptor pairs can be either attractive or repulsive, depending on the identity of the molecules and the context in which they signal the growth cone. (A) Extracellular matrix molecules serve as the ligands for multiple integrin receptors. (B) Homophilic, Ca^{2+}-independent cell adhesion molecules (CAMs) are at once ligands and receptors. (C) Ca^{2+}-dependent adhesion molecules, or cadherins, are also capable of homophilic binding. (D) The netrin/slit family of attractive and repulsive secreted signals acts through two distinct receptors, DCC ("*d*eleted in *c*olorectal *c*ancer"), which binds netrin, and robo, the receptor for slit. (E) Semaphorins are primarily repulsive cues that can either be bound to the cell surface or secreted. Their receptors (the plexins and neuropilin) are found on growth cones. (F) Ephrins, which can be transmembrane- or membrane-associated, signal via the Eph receptors, which are receptor tyrosine kinases.

fibronectin to integrins triggers a cascade of events—perhaps via interactions with cytoplasmic kinases and other soluble signaling molecules—that generally stimulates growth and elongation. These changes include fluctuations in levels of intracellular messengers such as calcium and inositol trisphosphate (IP_3), and the activation of additional intracellular kinase pathways

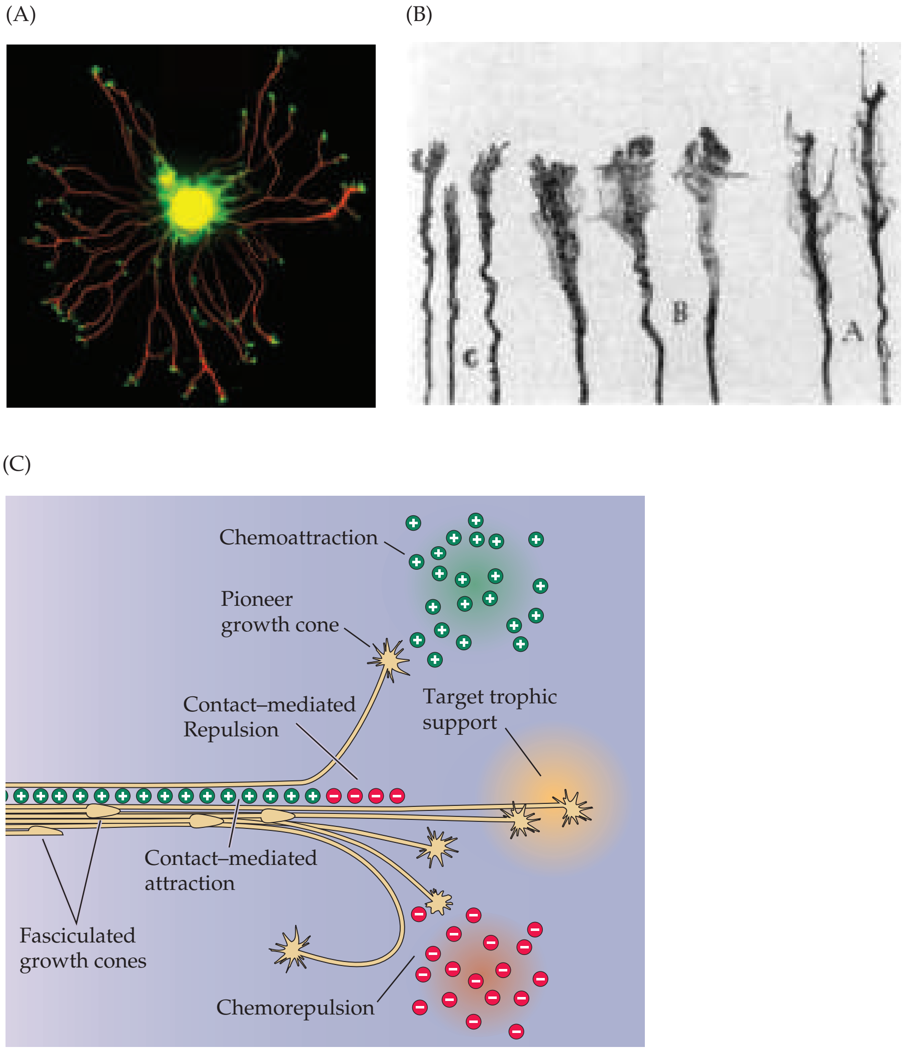


Figure 22.3 Growth cone interactions with the environment. (A) Potential classes of cues and their effects on growing axons. Attractant cues, either secreted or bound to the cell surface, can guide a growth cone to a particular domain, or help maintain growing axons as distinct bundles, or fascicles. (B) Growth cone morphology varies in a single axon pathway. Examples of axons at different points in their trajectory between the dorsal horn and the ventral midline. When the axons are growing in the dorsal spinal cord, the growth cones are simple, with few apparent filopodia. When these axons reach a "choice point" (presumably one rich in chemoattractant and repulsive cues) such as the floorplate at the ventral midline, the growth cones become more complex, with broader lamellapodia and multiple filopodial extensions. (C) Summary of growth cone responses to the range of cues available in the environment. (B courtesy of C. Mason; C after Huber et al., 2003.)

(see Chapter 7). The role of extracellular matrix molecules in axon guidance is particularly clear in the embryonic periphery. Axons extending through peripheral tissues grow through loosely arrayed mesenchymal cells that fill the interstices of the embryo, and the spaces between these mesenchymal cells are rich in extracellular matrix molecules. Axons also grow along the interface of mesenchyme and epithelial tissues including the epidermis, where an organized sheet of extracellular matrix components called the **basal lamina** provides a supportive substrate.

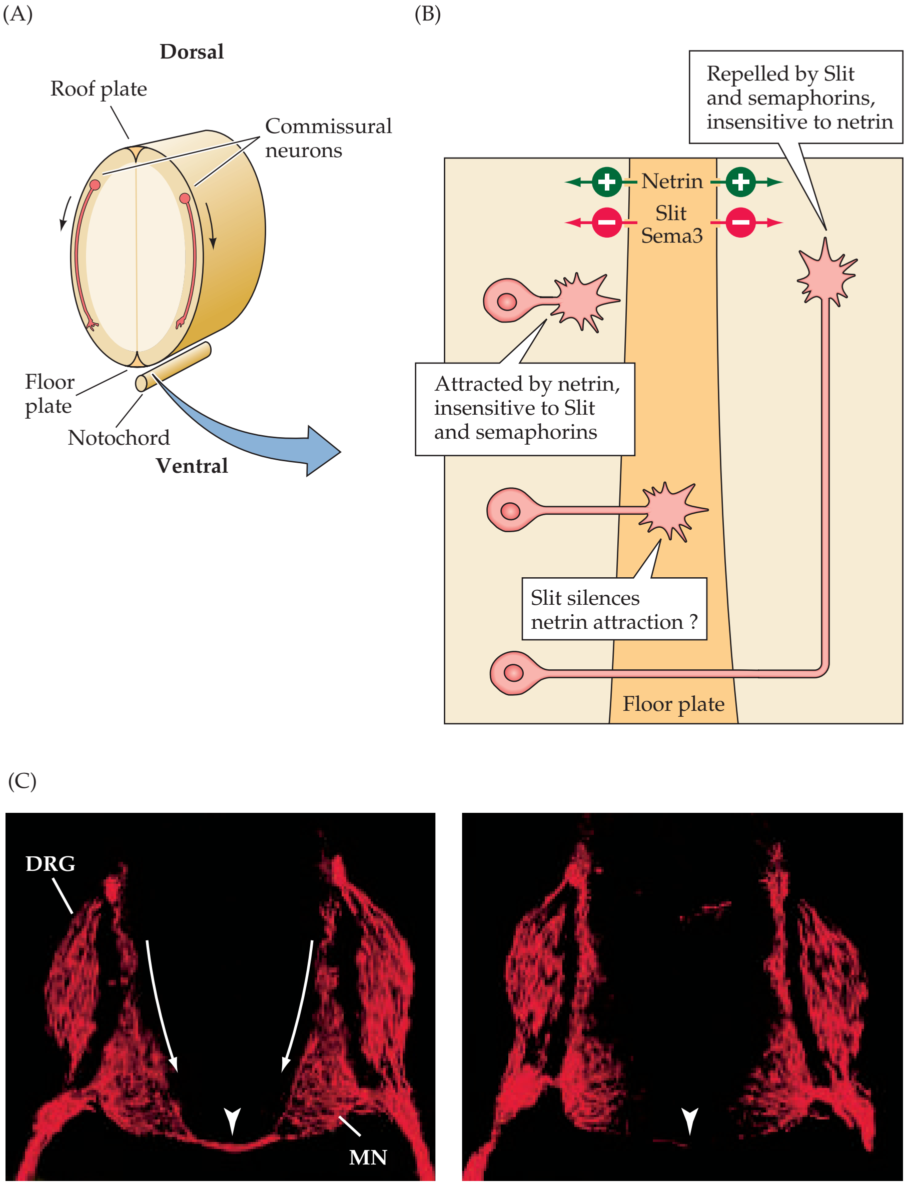
In addition, in peripheral nerves, matrix molecules are secreted by glial cells (Schwann cells) associated with growing axons. In tissue culture as well as in the embryo, different extracellular matrix molecules have different capacities to stimulate axon growth. Thus, the relative availability of different matrix molecules can influence the speed or direction of a growing axon. The role of matrix molecules in the central nervous system is less clear. Some of the same molecules are present in the extracellular space but are not organized into orderly substrates like the basal lamina in the periphery, and have therefore been harder to study.

The CAMs and cadherins are distinguished by their presence on both growing axons and growth cones as well as surrounding cells or targets (see Figure 22.3). Moreover, both CAMs and cadherins have dual functions as ligands and receptors, usually via homophilic binding. Some of the CAMs, especially the L1 CAM, have been associated with the bundling, or fasiculation, of groups of axons as they grow. Cadherins have been suggested as important determinants of final target selection in the transition from growing axon to synapse (see below). For both CAMs and cadherins, the unique ability of each class to function as both ligand and receptor (e.g., L1 is its own receptor) may be important for recognition between specific sets of axons and targets. Both these classes rely upon a somewhat indirect route of signal transduction. The Ca^{2+}-independent molecules interact with cytoplasmic kinases to initiate cellular responses, while the cadherins engage the APC/β-catenin pathway (also activated by Wnts; see Chapter 21).

The importance of adhesive interactions in axon growth and guidance mediated by these molecules is underscored by the pathogenesis of several inherited human developmental or neurological disorders. These syndromes—X-linked hydrocephalus, MASA (an acronym for *m*ental retardation, *a*phasia, *s*huffling gait, and *a*dducted thumbs), Kalman's syndrome (which compromises reproductive and chemosensory function) and X-linked spastic paraplegia—are all consequences of mutations in genes encoding cell surface adhesion molecules. These mutations can also lead to the absence of the corpus callosum, which connects the two cerebral hemispheres, and of the corticospinal tract, which carries cortical information to the spinal cord. Congenital anomalies such as these (which are fortunately rare) are now understood to arise from errors in the signaling mechanisms normally responsible for axon navigation via cell surface adhesion molecules.

Diffusible Signals for Axon Guidance: Chemoattraction and Repulsion

Another major challenge in establishing appropriate patterns of connectivity is attracting axons to distant targets, and insuring that the axons do not stray into inappropriate regions *en route*. Several additional molecules are responsible for this aspect of axon growth and guidance. With remarkable foresight, Cajal proposed early in the twentieth century that target-derived signals selectively influenced axonal growth cones, thereby attracting them to appropriate destinations. In addition to the chemoattraction predicted by Cajal, it was long supposed that there might also be chemorepellent signals that discouraged axon growth toward a particular region. Despite the clear importance of chemoattraction and repulsion in constructing pathways and circuits, the identity of the signals themselves remained uncertain until the last 15 years or so. One problem was the vanishingly small amounts of such factors expressed in the developing embryo. Another was that of distinguishing **tropic** molecules—which *guide* growing axons toward a source—from **trophic** molecules—which *support* the survival and growth of neurons and their processes once an appropriate target has been contacted (see below). These problems were solved by laborious biochemical purification and analysis of attractive or repulsive activities from vertebrate (chick) embryos, and genetic analysis of axon growth in both *Drosophila* and *C. elegans*; this work eventually led to the identification of several genes that code for chemotropic factors. Remarkably, the identity and function of chemoattractants and chemorepellents across phyla is highly conserved.


(A)
Dorsal
Roof plate
Commissural neurons
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Notochord
Ventral
(B)
Repelled by Slit and semaphorins, insensitive to netrin
Netrin
Slit
Sema3
Attracted by netrin, insensitive to Slit and semaphorins
Slit silences netrin attraction ?
Floor plate
(C)
DRG
MN

Figure 22.4 Chemotropic molecules (netrins) in the developing spinal cord. (A) Commissural neurons send axons to the ventral region of the spinal cord, including a specific region called the floorplate. (B) Opposing activities of netrin and slit at the ventral midline of the spinal cord. This molecular guidance system ensures that the axons relaying pain and temperature via the anterolateral pathway cross the midline at appropriate levels of the spinal cord and remain on the contralateral side until they reach their targets in the thalamus. (C) At left, labeled commissural axons (red) descend through the spinal cord, pass the motor column (MC), and cross the midline into the anterior (ventral) commissure of the spinal cord. At right, the netrin gene of a mouse has been homozygously inactivated, and the commissural axons do not fasciculate, nor do they cross at the ventral midline (arrowheads). (A after Serafini et al., 1994; B after Dickinson, 2002; C from Serafini et al., 1996.)

The best-characterized class of chemoattractant molecules is the **netrins** (from the Sanskrit "to guide"; Figure 22.4). In chick embryos, the netrins were identified as proteins with chemoattractant activity following biochemical purification. In *C. elegans*, netrins were first recognized as the product of a gene that influenced axon growth and guidance (the first such gene was called *Unc-6* for "uncoordinated," which describes the behavioral phenotype of the mutant worms; the cause is misrouted axons as a result of the absence of netrin). The netrins themselves have high homology to extracellular matrix molecules like laminin (see Figure 22.2) and in some cases may actually interact with the extracellular matrix to influence directed axon growth. Netrin signals are transduced by specific receptors including the molecule DCC (*d*eleted in *c*olorectal *c*ancer) as well as other co-receptors. Like many cell surface adhesion molecules, netrin receptors have repeated amino acid motifs in their extracellular domain, a transmembrane domain and an intracellular domain with no known enzymatic activity. Thus, there must be indirect routes of signal transduction following netrin binding to its receptor. Netrins are often found at the midline in the developing nervous system. Indeed, their initial characterization was guided by the observation that there seemed to be a chemoattractive signal in the spinal cord that influenced the growth of spinothalamic axons from the dorsal horn toward the ventral midline (see Figure 22.4). After their initial purification and cloning, netrins were localized to the floorplate, which defines the ventral midline in the developing spinal cord. Consistent with their expression and in vitro activity, mutation of the netrin-1 gene disrupts the development of the spinal cord anterior commissure as well as axon pathways that cross the midline in the forebrain: the corpus callosum, anterior commissure and hippocampal commissure. The secreted factor "slit" and its receptor "robo" (named for the phenotypes of *Drosophilia* mutants in which these genes were first identified) are important for preventing an axon from straying back over the midline once it has crossed initially in response to netrin. The combination of these molecules (and most likely others) and the relationships between their signaling pathways are thought to orchestrate the unidirectional crossing of axons at the midline—a process that is essential for the construction of some aspect of all major sensory, motor, and associational pathways in the mammalian brain.

Much of the research on axon guidance has focused on molecules that encourage axon outgrowth or attract growing neurons. Constructing the nervous system, however, also entails telling axons where *not* to grow. Two broad classes of chemorepellent molecules have been described. The first is associated with central nervous system myelin. These molecules—referred to as the **NoGo's**—and their receptors are evidently important after injury to the adult brain, where they inhibit axon growth at regions of CNS damage (see Chapter 24); however, their role in initial axon growth and guidance is less clear. In addition to the NoGo's, some protein components of the myelin sheath, including myelin basic protein, also can be chemorepulsive for growing axons. Molecules belonging to the second class of chemorepellents are active during neural development. These molecules, called **semaphorins** (*semaphor* is the Greek word for "signal"; see Figure 22.2E), are eventually bound to cell surfaces or to the extracellular matrix, where they can prevent the extension of nearby axons (Figure 22.5). Their receptors, like those for cell surface adhesion molecules, are transmembrane proteins (including the plexins and a protein called neuropilin) whose cytoplasmic domains have no known catalytic activity, but can complex with intercellular kinases and other signaling molecules.

Much of the initial characterization of semaphorin chemorepellent activity emerged from studies of invertebrates—particularly *Drosophila*—where mutation or manipulation of these genes can cause axons to grow abnormally. Studies with cultured vertebrate neurons indicated that the semaphorins can cause collapse of growth cones and cessation of axon extension. The activity of these molecules in developing vertebrates, however, has been harder to demonstrate in vivo. For example, inappropriate growth or targeting of axons is not apparent when single semaphorin genes are deleted in mice; nevertheless, local introduction of semaphorins can lead to altered axon trajectories due to avoidance of the exogenous semaphorin. The semaphorins represent the largest family of chemorepellants. None of these molecules alone, however, explains the initial choices and resulting trajectories of developing axons. It is nonetheless clear that the semaphorins make an

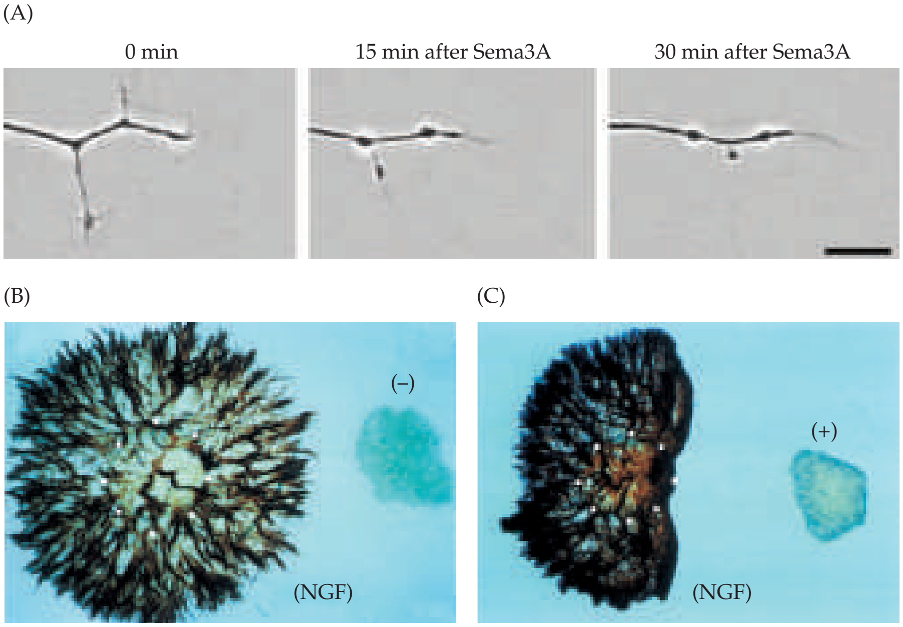


Figure 22.5 Semaphorins promote growth cone collapse and axon repulsion. (A) Time-lapse series showing a growth cone exposed to semaphorin. (B) In the presence of nerve growth factor (NGF), explant cultures of chick dorsal root ganglia extend halos of neurites that originate from different neuronal subpopulations. (C) Co-culture of a ganglion with non-neuronal cells (+) transfected with the gene for semaphorin III (collapsin) results in asymmetrical growth of the ganglion cell neurites as a result of chemorepulsion. Control cells not transfected with the gene [(–) in panel B] have no effect on the pattern of outgrowth. (A from Dontchev and Letourneau, 2002; B, C from Messersmith et al., 1995.)

important contribution to the orderly construction of axon pathways in both the periphery and in the central nervous system.

The Formation of Topographic Maps

In the somatic sensory, visual, and motor systems, neuronal connections are arranged such that neighboring points in the periphery are represented at similarly adjacent locations in the appropriate regions of the central nervous system (see Chapters 8, 11, and 16). In other systems (e.g., the auditory and olfactory systems), there are also orderly representations of various stimulus attributes like frequency or receptor identity. How do growing axons distribute themselves with such fidelity within target regions in the brain?

In the early 1960s, Roger Sperry, who later did pioneering work on the functional specialization of the cerebral hemispheres (see Chapter 26), articulated the **chemoaffinity hypothesis**, based primarily on work in the visual system of frogs and goldfish. In these animals, the terminals of retinal ganglion cells form a precise topographic map in the optic tectum (the tectum is homologous to the mammalian superior colliculus). When Sperry crushed the optic nerve and allowed it to regenerate (fish and amphibians, unlike mammals, can regenerate axonal tracts in their central nervous system; see Chapter 24), he found that retinal axons reestablished the same pattern of connections in the tectum. Even if the eye was rotated 180°, the regenerating axons grew back to their original tectal destinations (causing some behavioral confusion for the frog: Figure 22.6B). Accordingly, Sperry proposed that each tectal cell carries an "identification tag"; he further supposed that the growing terminals of retinal ganglion cells have complementary tags, such that they seek out a specific location in the tectum. In modern parlance, these "chemical" tags are cell adhesion or recognition molecules, and the "affinity" that they engender is a selective binding of receptor molecules on the growth cone to corresponding molecules on the tectal cells that signal their relative positions.

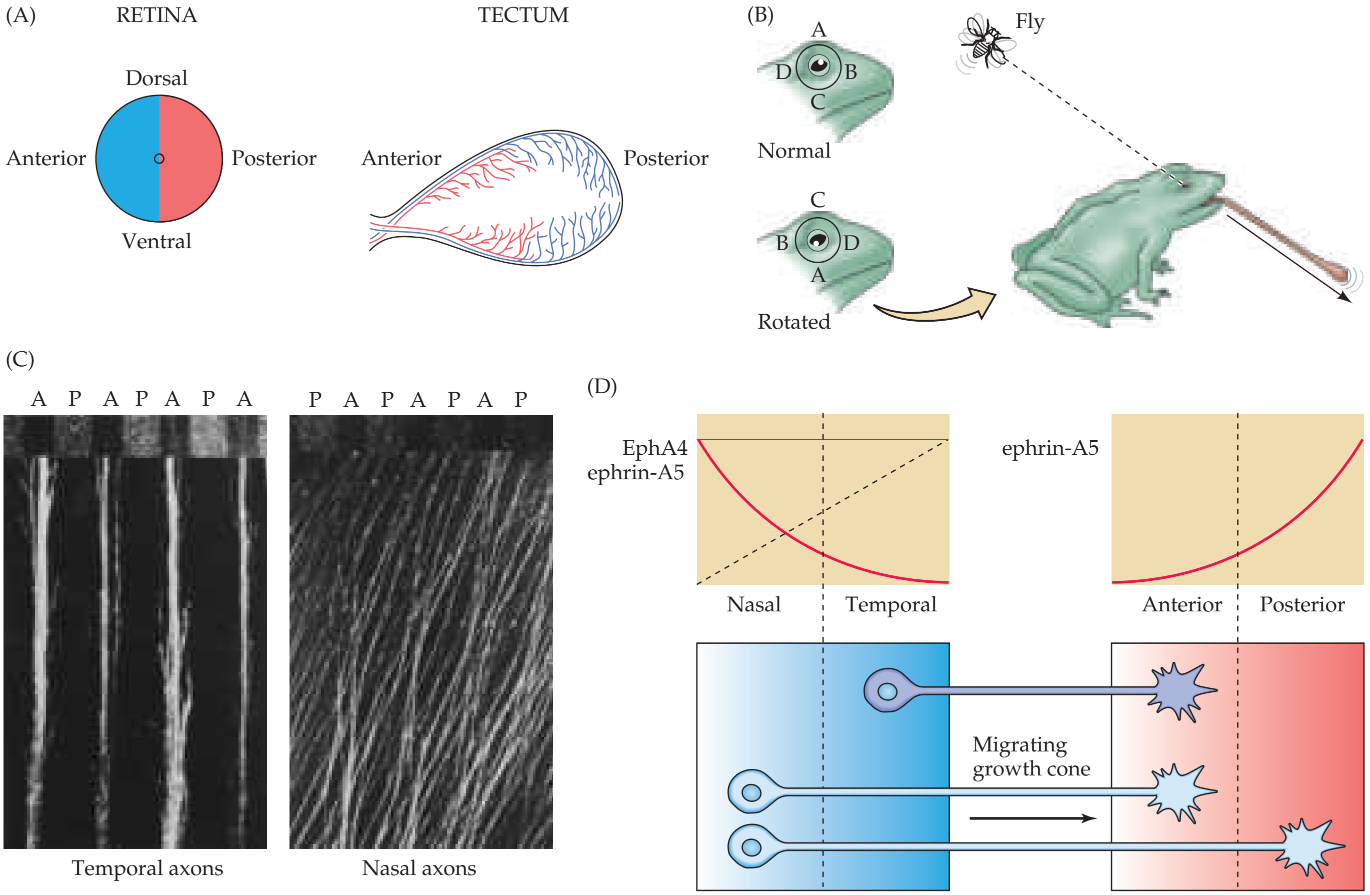

(A)
RETINA
TECTUM
Dorsal
Anterior
Posterior
Ventral
Anterior
Posterior
(B)
A
D
B
C
Normal
C
B
D
A
Rotated
Fly
(C)
A P A P A P A
P A P A P A P
Temporal axons
Nasal axons
(D)
EphA4
ephrin-A5
Nasal
Temporal
ephrin-A5
Anterior
Posterior
Migrating
growth cone

Figure 22.6 Mechanisms of topographic mapping in the vertebrate visual system. (A) Posterior retinal axons project to the anterior tectum and anterior retinal axons to the posterior tectum. When the optic nerve of a frog is surgically interrupted, the axons regenerate with the appropriate specificity. (B) Even if the eye is rotated after severing the optic nerve, the axons regenerate to their original position in the tectum. This topographic constancy is evident from the frog's behavior: When a fly is presented above, the frog consistently strikes downward, and vice versa. (C) An in vitro assay for cell surface molecules that contribute to topographic specificity in the optic tectum. A set of alternating stripes (90 µm wide) of membranes from anterior (A) and posterior (P) optic tectum of chicks was laid down on a glass coverslip. The posterior membranes have fluorescent particles added to make the boundaries of the stripes apparent (top of panels). Explants of retina from either nasal or temporal retina were placed on the stripes. Temporal axons prefer to grow on anterior membranes and are repulsed by posterior membranes. In contrast, nasal retinal axons grow equally well on both stripes. (D) Complementary gradients of Eph receptors (in afferent cells and their growth cones) and ephrins (in the target cells) lead to differential affinities and topograpic mapping. In this model, a growth cone with a high concentration of Eph receptors would be more likely to recognize a lower concentration of ligand, whereas a growth cone with low Eph receptor concentration would recognize a higher concentration of ligand. (A, B after Sperry, 1963; C from Walter et al., 1987; D after Wilkinson, 2001.)

Further experiments in the amphibian and avian visual systems made the strictest form of the chemoaffinity hypothesis—labeling of each tectal location by a different recognition molecule—untenable. Rather than precise "lock and key" affinity, the behavior of growing axons suggested that there are gradients of cell surface molecules to which growing axons respond to establish the basic axes of the retinotopic map. Normally, axons from the temporal region of the retina innervate the anterior pole of the tectum and avoid the posterior pole. Embryological experiments in which temporal and nasal regions of the retina or anterior and posterior regions of the tectum were reversed in their position suggested that there was some specificity. This specificity, however, was not absolute—if only posterior tectum was available to temporal retina axons, the axons would innervate the normally inhospitable target. Subsequent in vitro analysis showed that the specificity was generated by a comparison between different substrates. Temporal retinal axons, when presented with a choice of cell membranes derived from anterior or posterior tectal regions as a substrate, grow exclusively on anterior membranes, avoiding membranes derived from the "wrong" region of the tectum (Figure 22.6C). The positive interactions probably are due to increased adhesion of the growth cones to the substrate, whereas the failure to grow into inappropriate regions may result from repulsive interactions that tend to collapse the growth cones (see above).

A likely candidate for the negative guidance signal for temporal axons in the posterior tectum was subsequently purified, and its gene cloned. The protein—initially called RAGS (*r*epulsive *a*xon *g*uidance *s*ignal) and later renamed ephrin-A5—belongs to a family of **ephrin ligands** and **Eph receptors** (see Figure 22.2). Subsequent work has associated several members of this molecular family with topographic mapping in the visual system as well as formation of axon pathways like the anterior commissure and migration of subpopulations of neural crest cells (Figure 22.6D). Ephrin ligands are cell adhesion-like molecules that can be either transmembrane or membrane-associated proteins. Eph receptors belong to the single transmembrane domain tyrosine receptor kinase family, and thus can directly transduce a signal from an Eph ligand. Subsequent work has also suggested that the Ephrin ligands can generate intercellular signals upon binding with the Eph receptors via interactions with cytoplasmic kinases and related molecules. Disruption of the genes for the Eph ligands or their receptors results in subtle disruptions in the topographic organization of the retinocollicular or retinothalamic projection. These observations accord with the idea that chemoaffinity operates by a system of gradients in the retina and tectum that give axons and their targets markers of position, rather than a unique lock and key sort of recognition. The Eph receptors and their ligands provide a model of how graded molecular information can help organize topographic axonal growth in the visual system and other regions of the developing brain.

Selective Synapse Formation

After reaching the correct target or target region, axons must make a further local determination about which particular cells to innervate among a variety of potential local synaptic partners. The choices available to an axon include: establish synaptic contacts; retract and regrow to another target; or fail to form stable connections (a choice that can result in the death of the parent neuron). Because of the complexity of brain circuitry, this issue has been studied most thoroughly in the peripheral nervous system, particularly

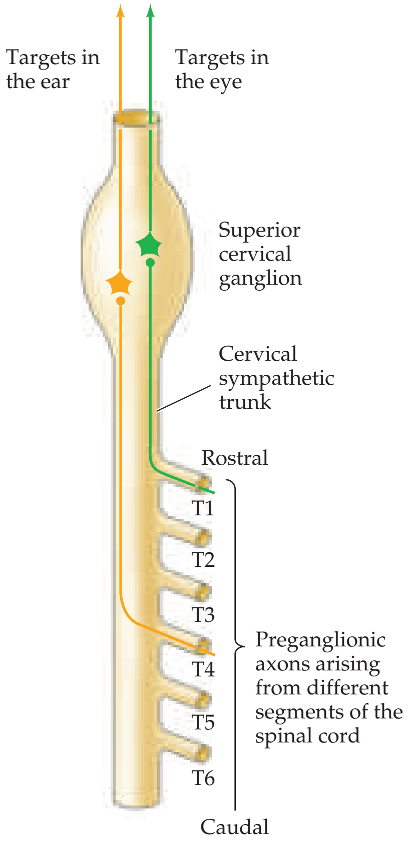

Targets in the ear
Targets in the eye
Superior cervical ganglion
Cervical sympathetic trunk
Rostral
T1
T2
T3
T4
T5
T6
Caudal
Preganglionic axons arising from different segments of the spinal cord

Figure 22.7 Evidence that synaptic connections between mammalian neurons form according to specific affinities between different classes of pre- and postsynaptic cells. In the superior cervical ganglion, preganglionic neurons located in particular spinal cord segments (T1, for example) innervate ganglion cells that project to particular peripheral targets (the eye, for example). Establishment of these preferential synaptic relationships indicates that selective neuronal affinities are a major determinant of neural connectivity.

in the innervation of muscle fibers (Box B) and autonomic ganglion cells by spinal cord motor neurons. Synaptic specificity was first explored by British physiologist John Langley at the end of the nineteenth century. Preganglionic sympathetic neurons located at different levels of the spinal cord innervate cells in sympathetic chain ganglia in a stereotyped and selective manner (Figure 22.7; see also Chapter 20). In the superior cervical ganglion, for example, cells from the highest thoracic level (T1) innervate ganglion cells that project in turn to targets in the eye, whereas neurons from a somewhat lower level (T4) innervate ganglion cells that cause constriction of the blood vessels of the ear. Since the axons of all these neurons run together in the cervical sympathetic trunk to arrive at the ganglion, the mechanisms underlying the differential innervation of the ganglion cells must occur at the level of synapse formation rather than axon guidance to the general vicinity of target cells (see above). Anticipating Sperry by more than 50 years in a different context, Langley concluded that selective synapse formation is based on differential affinities of the pre- and postsynaptic elements.

Subsequent studies based on intracellular recordings from individual neurons in the superior cervical ganglion have shown, however, that the selective affinities between pre- and postsynaptic neurons are not especially restrictive. Thus, synaptic connections to ganglion cells made by preganglionic neurons of a particular spinal level are preferred, but synaptic contacts from neurons at other levels are not excluded (much like the rules that govern axon guidance). Furthermore, if the innervation to the superior cervical ganglion from a particular spinal level is surgically interrupted, recordings made some weeks later indicate that new connections are established by residual axons arising from what would normally be inappropriate spinal segments. The novel connections also establish a pattern of segmental preferences, as if the system had attempted to achieve the best match it could under the altered circumstances. Despite this relative selectivity during synapse formation, a quite different line of work has shown that *where* a synapse forms on the target cell (at least if the cell is a muscle fiber) is tightly controlled by a set of molecules that are now understood in some detail (see Box B). Perhaps not surprisingly, these molecules include variants of several of the cell adhesion molecules that influence growth cone behavior (see below).

There are some absolute restrictions to synaptic associations. Thus, neurons do not innervate nearby glial or connective tissue cells, and many instances have been described in which various nerve and target cell types show little or no inclination to establish connections with one another. When synaptogenesis does proceed, however, neurons and their targets in both the central and peripheral nervous systems appear to associate according to a continuously variable system of preferences—much like the old song "if you can't be with the one you love, love the one you're with." Such biases guide the pattern of innervation that arises in development (or reinnervation) without limiting it in any absolute way. The target cells residing in muscles, autonomic ganglia, or elsewhere are certainly not equivalent, but neither are they unique with respect to the innervation they can receive. This relative promiscuity can cause problems following neural injury, since regenerated patterns of peripheral innervation are not always appropriate (see Chapter 24).

Several observations show that many of the same adhesion molecules that participate in axon guidance contribute to the identification and stabilization of a synaptic site on target cells, as well as to the ability of a growing axon to recognize specific sites as optimal. Ephrins have been suggested to contribute to this process, as have cadherins. In both cases the diversity of ligands and receptors makes these adhesion molecule families attractive candidates. This speculation has an intriguing parallel in *Drosophila*. In the fly, the gene for the cell adhesion molecule DSCAM (the fly ortholog of the mammalian *d*own *s*yndrome *c*ell *a*dhesion *m*olecule, the gene for which is located on chromosome 21, the chromosome that is duplicated in Down syndrome) has approximately 38,000 isoforms based upon the numbers of exons in the gene and predicted splicing (Figure 22.8A). In the fly, DSCAM is expressed at synaptic sites in the developing nervous system. It is not yet clear whether or not individual splice isoforms are differentially expressed at distinct synaptic sites; however, if this is the case, the genomic diversity may contribute

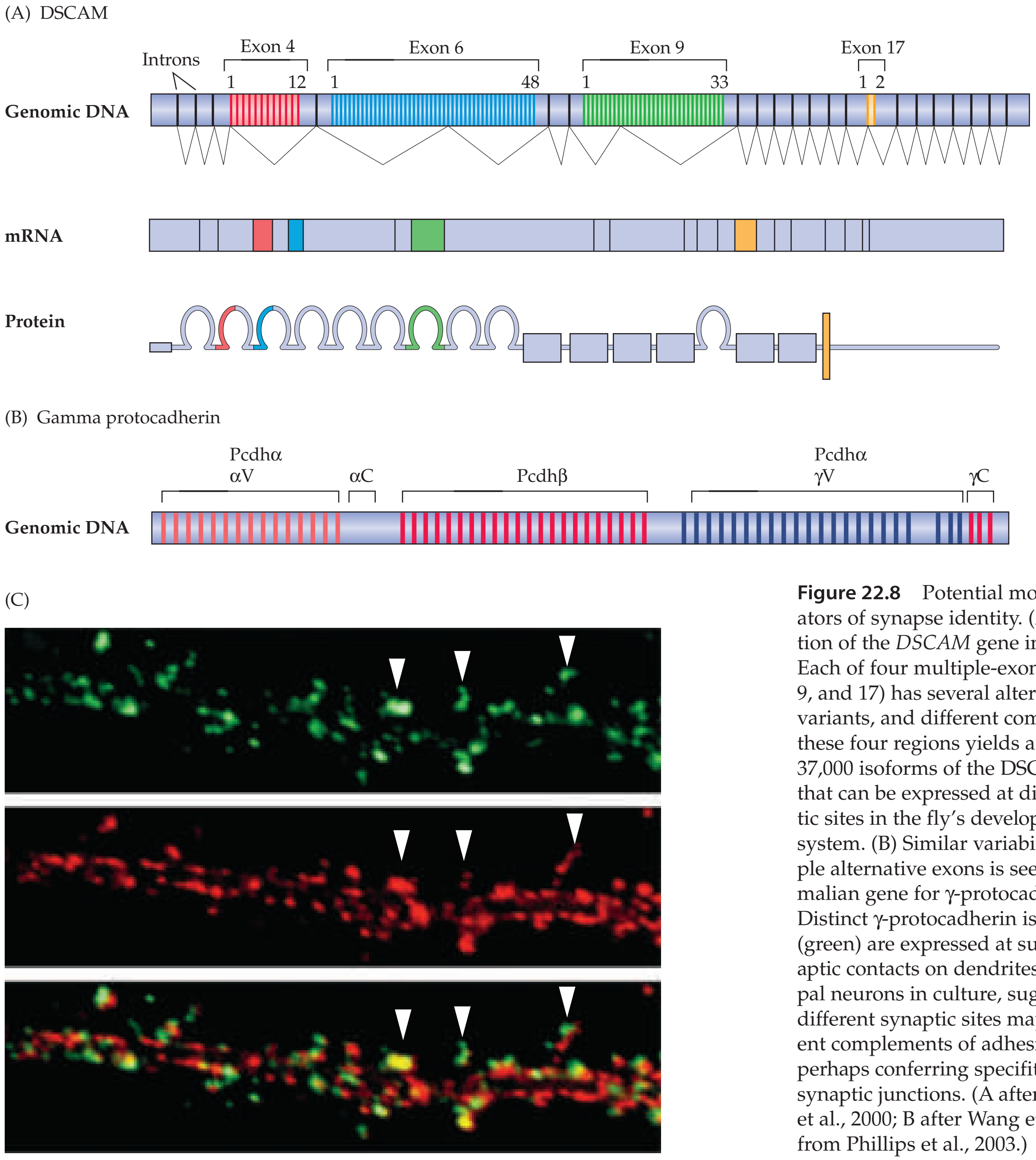


Figure 22.8 Potential molecular mediators of synapse identity. (A) Organization of the *DSCAM* gene in *Drosophila.* Each of four multiple-exon regions (4, 6, 9, and 17) has several alternative splice variants, and different combinations of these four regions yields a potential 37,000 isoforms of the DSCAM protein that can be expressed at distinct synaptic sites in the fly's developing nervous system. (B) Similar variability of multiple alternative exons is seen in the mammalian gene for γ-protocadherin. (C) Distinct γ-protocadherin isoforms (green) are expressed at subsets of synaptic contacts on dendrites of hippocampal neurons in culture, suggesting that different synaptic sites may have different complements of adhesion molecules perhaps conferring specifity to those synaptic junctions. (A after Schmucker et al., 2000; B after Wang et al., 2002; C from Phillips et al., 2003.)

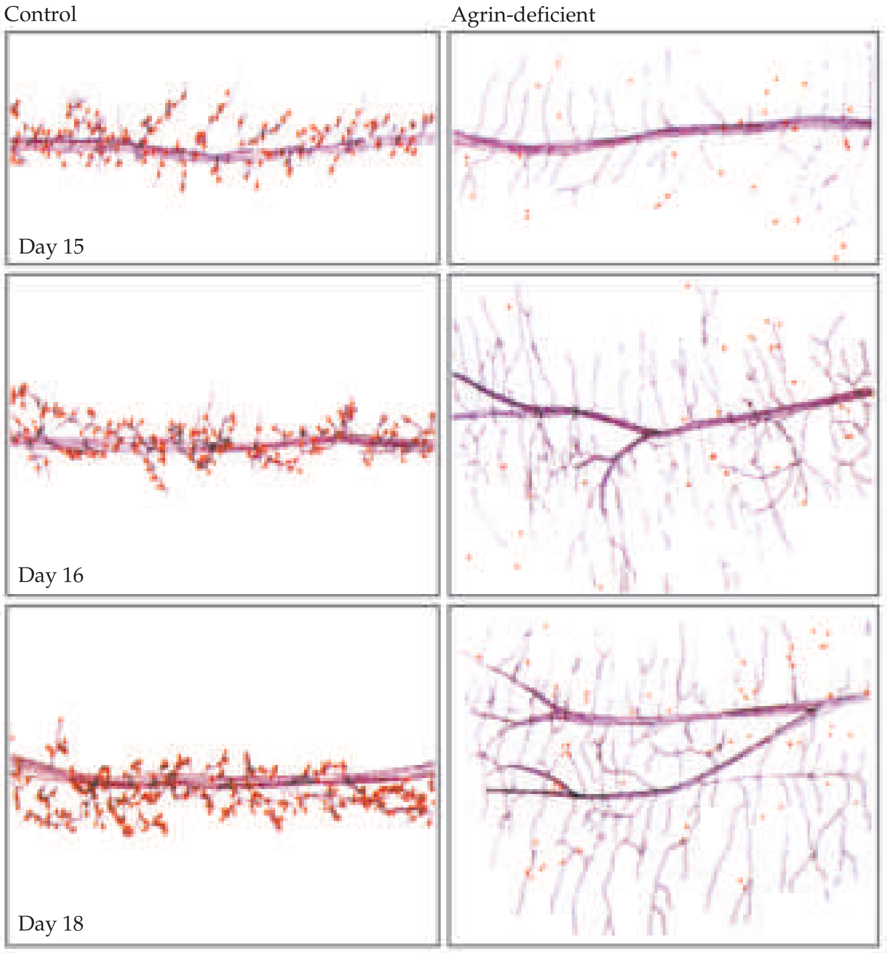
Box B

Molecular Signals That Promote Synapse Formation

Synapses require a precise organization of presynaptic and postsynaptic elements in order to function properly (see Chapters 4–7). At the neuromuscular junction, for example, synaptic vesicles and the related release machinery are located at sites in the nerve terminal called active zones; and, in the postsynaptic muscle cell, acetylcholine receptors and other synapse-specific molecules are localized in high density exactly subjacent to the presynaptic active zones. During the past 25 years, a number of investigators have identified some of the molecular cues that guide the formation of these carefully apposed elements. Their efforts have met with the greatest success at the neuromuscular junction, where a molecule called agrin is now known to be responsible for initiating some of the events that lead to the formation of a fully functional synapse.

Agrin was originally identified as a result of its influence in the reinnervation of frog neuromuscular junctions following damage to the motor nerve. In mature skeletal muscle, each fiber typically receives a single synaptic contact at a highly specialized region called the end plate (see Chapter 5). U. J. McMahan, Josh Sanes, and their colleagues at Harvard and later Stanford and Washington Universities found that regenerating axons reinnervate the original end plate site precisely. In seeking to determine the molecular signals underlying this phenomenon, they took advantage of the fact that each muscle fiber is surrounded by a sheath of extracellular matrix called the basal lamina. When muscle fibers degenerate, they leave the basal lamina behind (as do degenerating axons); moreover, a specific infolding of the basal lamina at the former end plate site allows its continued identification. Remarkably, presynaptic nerve terminals differentiate at these original sites even when the associated muscle fibers are absent. Equally remarkable is that regenerating muscle fibers form postsynaptic specializations—such as densely packed acetylcholine receptors—at precisely these same basal lamina locations in the absence of nerve fibers! These findings show that the signal(s) guiding synapse formation remain in the extracellular environment after removal of either nerve or muscle, presumably in the basal lamina "ghost" that surrounds each muscle fiber.

Using a bioassay based on the aggregation of acetylcholine receptors to analyze the constituents of the basal lamina,



Development of neuromuscular junctions in agrin-deficient mice. Diaphragm muscles from control (left) and agrin-deficient (right) mice at embryonic day 15, 16, and 18 were double-stained for acetylcholine receptors and axons, then drawn with a camera lucida. The developing muscle fibers run vertically. In both control and mutant muscles, an intramuscular nerve (black) and aggregates of AChRs (red) are present by embryonic day 15. In controls, axonal branches and AChR clusters are confined to a band at the central end plate at all stages. Mutant AChR aggregates are smaller, less dense, and less numerous; axons form fewer branches and their synaptic relationships are disorganized. (From Gautam et al., 1996.)

McMahan and colleagues isolated and purified agrin. Agrin is a proteoglycan found in both mammalian motor neurons and muscle fibers; it is also abundant in brain tissue. The neuronal form of agrin is synthesized by motor neurons, transported down their axons, and released from growing nerve fibers. Agrin binds to a postsynaptic receptor whose activation leads to a clustering of acetylcholine receptors and, evidently, to subsequent events in synaptogenesis. Support for the role of agrin as an organizer of synaptic differentiation is the finding by Sanes and his collaborators that genetically engineered mice that lack the gene for agrin develop in utero with few neuromuscular junctions (see figure). Importantly, mice lacking only neural agrin were as severely impaired as mice lacking both nerve and muscle agrin. Animals missing the agrin receptor also fail to develop neuromuscular junctions and die at birth. Agrin is therefore one of the first examples of a presynaptically derived molecule that promotes postsynaptic differentiation in target cells.

Because synapse formation requires an ongoing dialogue between pre- and postsynaptic partners, it is likely that postsynaptically derived organizers of presynaptic differentiation also exist. Based on the studies of basal lamina mentioned above, Sanes and his collaborators identified one such group of molecules, the β2-laminins (originally called s-laminin). Mice lacking β2-laminin show deficits in differentiation of motor nerve terminals and, unexpectedly, of terminal-associated glial (Schwann) cells. However, presynaptic defects in β2-laminin mutants are considerably less severe than postsynaptic defects in agrin mutants, suggesting that additional important retrograde signals remain to be identified.

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to synaptic diversity. While the mammalian orthologue of DSCAM does not show a similar diversity, some members of the protocadherin family do (Figure 22.8B,C). The possibility that protocadherin splice isoforms might invest synaptic sites with unique identities has thus been raised.

Trophic Interactions and the Ultimate Size of Neuronal Populations

The formation of synaptic contacts between growing axons and their synaptic partners marks the beginning of a new stage of development. Once synaptic contacts are established, neurons become dependent in some degree on the presence of their targets for continued survival and differentiation; in the absence of synaptic targets, the axons and dendrites of developing neurons atrophy and the innervating nerve cells may eventually die. This long-term dependency between neurons and their targets is referred to as **trophic interaction**. The word *trophic* is taken from the Greek *trophé*, meaning, roughly, "nourishment." Despite this nomenclature, the sustenance provided to neurons by trophic interactions is not the sort derived from metabolites such as glucose or ATP. Rather, the dependence is based on specific signaling molecules called **neurotrophic factors**. Neurotrophic factors, like some other intercellular signaling molecules (mitogens and cytokines, for example), originate from target tissues and regulate neuronal differentiation, growth, and ultimately survival. These factors (referred to as **neurotrophins**

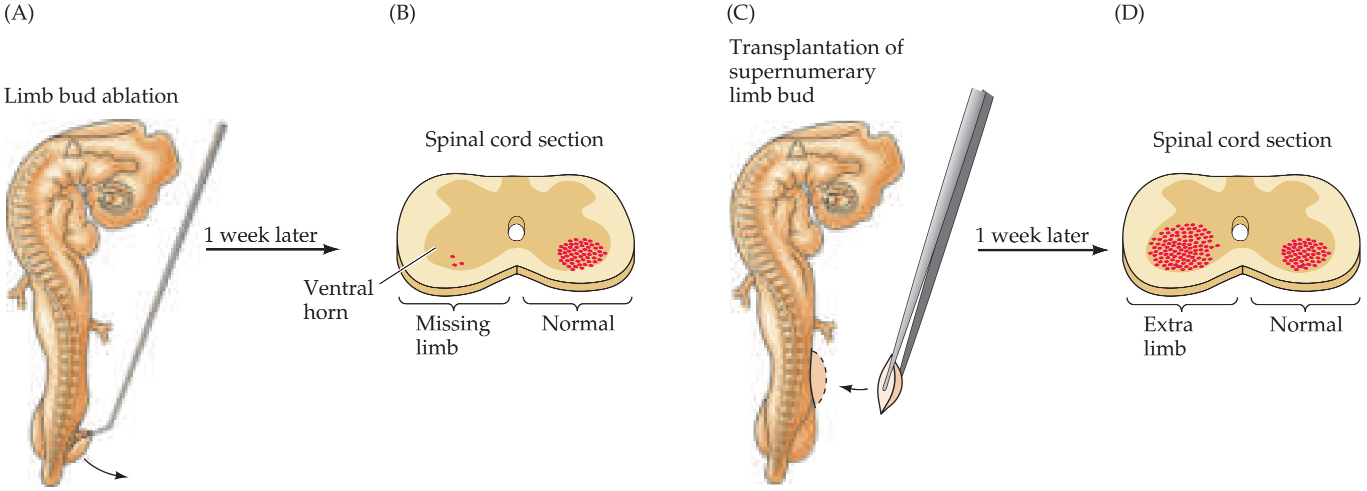


Figure 22.9 Effect of removing or augmenting neural targets on the survival of related neurons. (A) Limb bud amputation in a chick embryo at the appropriate stage of development (about 2.5 days of incubation) depletes the pool of motor neurons that would have innervated the missing extremity. (B) A cross section of the lumbar spinal cord in an embryo that underwent this surgery about a week earlier. The motor neurons (dots) in the ventral horn that would have innervated the hindlimb degenerate almost completely after embryonic amputation; a normal complement of motor neurons is present on the other side. (C) Adding an extra limb bud before the normal period of cell death rescues neurons that normally would have died. (D) Such augmentation leads to an abnormally large number of limb motor neurons (dots) on the side related to the extra limb. (After Hamburger, 1958, 1977, and Hollyday and Hamburger, 1976.)

for short) are unique in that, unlike inductive signaling molecules and cell adhesion molecules, their expression is limited primarily to neurons as well as some non-neural targets like muscles, and they are first detected after the initial populations of postmitotic neurons have been generated in the nascent central and peripheral nervous systems.

Why should neurons depend so strongly on their targets, and what specific cellular and molecular interactions mediate this dependence? The answer to the first part of this question lies in the changing scale of the developing nervous system and the body it serves, and the related need to precisely match the number of neurons in particular populations with the size of their targets. The basic mechanisms by which neurons are initially generated have already been considered in Chapter 21. There is, however, one more issue in generating the final complement of neurons. A general—and surprising—strategy in the development of vertebrates is the production of an initial surplus of nerve cells (on the order of two- or threefold); the final population is subsequently established by the death of those neurons that fail to interact successfully with their intended targets (see below). The elimination of supernumerary neurons is now known to be mediated by neurotrophic factors.

Evidence that targets play a major role in determining the size of the neuronal populations that innervate them has come from an ongoing series of studies dating from the start of the twentieth century. The seminal observation was that the removal of a limb bud from a chick embryo results, at later embryonic stages, in a striking reduction in the number of nerve cells (α motor neurons) in the corresponding portions of the spinal cord (Figure 22.9A,B). These supernumerary neurons die due to a lack of trophic support. The interpretation of these experiments is that neurons, in the spinal cord in this case, compete with one another for a resource present in the target (the developing limb) that is available in limited supply. In support of this idea, many neurons that would normally have died can be rescued by augmenting the amount of target available—in this example, by adding another limb that can be innervated by the same spinal segments that innervate the normal limb—thereby providing extra trophic support (Figure 22.9C,D). Thus, the size of nerve cell populations in the adult is not fully determined in advance by a rigid genetic program. It can be modified by idiosyncratic neuron–target interactions in each developing individual.

Further Competitive Interactions in the Formation of Neuronal Connections

Once neuronal populations are established by this winnowing, trophic interactions continue to modulate the formation of synaptic connections, beginning in embryonic life and extending far beyond birth. Among the problems that must be solved during the establishment of innervation is ensuring that each target cell is innervated by the right number of axons, and that each axon innervates the right number of target cells. Getting these numbers right is another major achievement of trophic interactions between developing neurons and target cells, and is necessary for establishing appropriate circuits to support specific functional demands of each individual organism.

Studying synaptic refinement in the complex circuitry of the cerebral cortex or other regions of the central nervous system is a formidable challenge. As a result, many basic ideas about the ongoing modification of developing brain circuitry have come from simpler, more accessible systems, most notably the vertebrate neuromuscular junction and autonomic ganglion cells (Figure 22.10). Adult skeletal muscle fibers and neurons in some classes of autonomic ganglia (parasympathetic neurons) are each innervated by a single axon. Initially, however, each of these target cells is innervated by axons from several neurons, a condition termed **polyneuronal innervation**. In such cases, inputs are gradually lost during early postnatal development until only one remains. This process of loss is generally referred to as **synapse elimination**, although the elimination actually refers to a reduction in the number of different axonal *inputs* to the target cells, not to a reduction in the overall number of synapses made on the postsynaptic cells. In fact, the overall number of *synapses* (individual specialized sites for release of neurotransmitter) in the peripheral nervous system increases steadily during the course of develop-

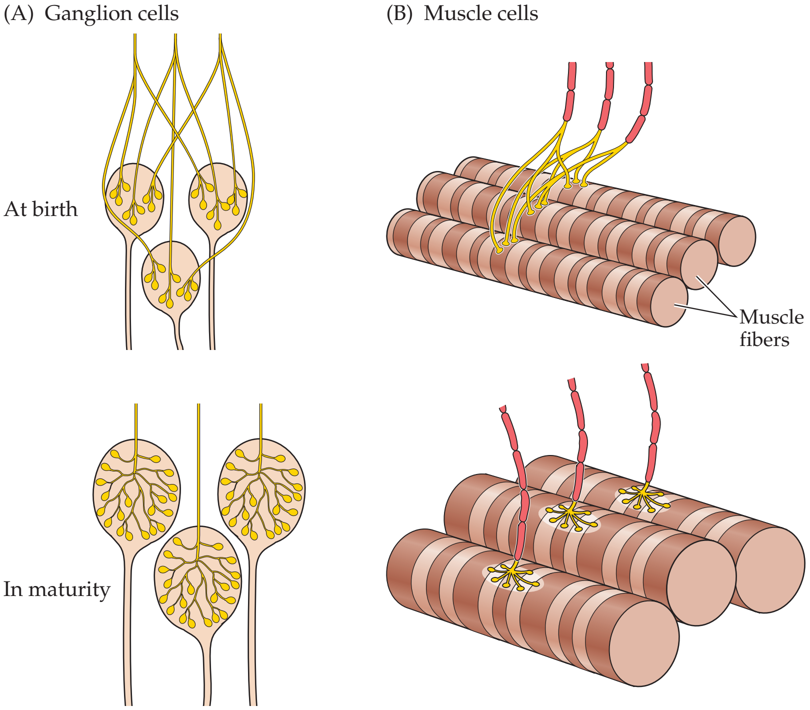


Figure 22.10 Major features of synaptic rearrangement during the first few weeks of postnatal life in the mammalian peripheral nervous system. In ganglia comprising neurons without dendrites (A) and in muscles (B), each axon innervates more target cells at birth than in maturity. In both muscles and ganglia, however, the size and complexity of the terminal arbor on each target cell increases. Thus, each axon elaborates more and more terminal branches and synaptic endings on the target cells it will innervate in maturity. The common denominator of this process is not a net loss of synapses, but the focusing by each axon of a progressively increasing amount of synaptic machinery on fewer target cells. (After Purves and Lichtman, 1980.)

ment, as is the case throughout the brain. A variety of experiments have shown that the elimination of some initial inputs to muscle and ganglion cells is a process in which synapses originating from different neurons compete with one another for "ownership" of an individual target cell (see Box B).

Importantly, such competition is thought to be modulated by patterns of electrical activity in the pre- and postsynaptic partners. For example, if acetylcholine receptors at the neuromuscular junction are blocked by curare (a potent antagonist of the acetylcholine receptor; see Chapter 6), polyneuronal innervation persists. Blocking presynaptic action potentials in the motor neuron axons (by silencing the nerve with tetrodotoxin, a sodium channel blocker) also prevents the reduction of polyneuronal innervation. Blocking neural activity, therefore, reduces (or delays) competitive interactions and the associated synaptic rearrangements.

The object of this competition is not known. Some of the phenomena of activity-dependent competition in muscles and autonomic ganglia (as well as in more complex central nervous system structures) could be explained by postulating that (1) synapses require a certain minimal level of trophic support to persist, (2) the relevant factors are secreted in limited amounts by the postsynaptic (target) cells in response to synaptic activation, and (3) synapses can only avail themselves of trophic support if their activity and that of the target cell coincide. There is, however, little direct evidence for this scenario. Equally plausible is the idea that active synapses provide a destabilizing signal that weakens asynchronously firing inputs. Thus, how activity achieves its effects on synaptic connectivity remains a key question.

The most useful insights into the nature of synaptic rearrangement during development have come from direct observation of this process (Figure 22.11). Using different-colored fluorescent dyes that stain either the presynaptic terminal or the postsynaptic receptors synaptic rearrangement Jeff Lichtman and his colleagues have followed the same neuromuscular junction over days, weeks, or longer. These observations have yielded some unexpected results. Competition between synapses arising from different motor neurons does not involve the active displacement of the "losing" input by the eventual "winner." Instead, it appears that the inputs of the two competitors gradually segregate. The "losing" axon then atrophies and retracts from the synaptic site. This is accomplished by a loss of the corresponding postsynaptic specializations associated with the "loser." Neurotransmitter receptors beneath the terminal branches that eventually will be eliminated are also lost. This receptor loss occurs before the nerve terminal

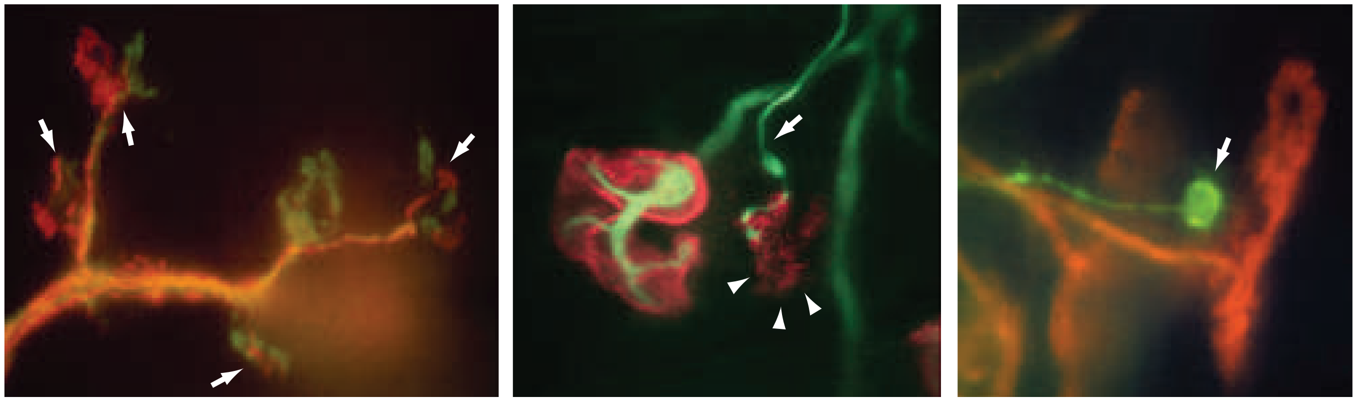


Figure 22.11 Synapse elimination at neuromuscular junctions. (A) Several neuromuscular junctions (arrows) from a mouse fetus (embryonic day 17). The red and green terminals are synapses from two different axons that converge at each of several junctions. (B) A single neuromuscular junction at higher magnification during a late stage of competition in which one of the synaptic inputs is close to elimination (white arrow). The "losing" input has completely segregated from the other axon, and the synaptic area on the muscle fiber that it occupies (labeled red with an acetylcholine antibody) is disappearing as the nerve is being eliminated (arrowheads). (C) This image illustrates the outcome of synaptic competition just after the losing axon (green) has withdrawn, leaving a red axon and its terminal. Note that the "loser" (green axon) has a retraction bulb at the end (arrow), and the "winning" axon (red) is significantly thicker. (Courtesy of J. W. Lichtman.)

has withdrawn and presumably reduces the synaptic strength of the input, which causes a further loss of postsynaptic receptors, leading to further reduction in the strength of the input. The downward spiral of synaptic efficacy presumably results in withdrawal of the presynaptic terminal. The remaining terminals then continue to enlarge and strengthen in place as the end plate region expands during postnatal muscle growth.

A generally similar reorganization of synaptic innervation is evident in a variety of other peripheral and central nervous system regions. In the peripheral nervous system, the number of presynaptic axons innervating each neuron can also decrease, as demonstrated by studies of certain autonomic ganglia. A similar process has been described in the central nervous system. In the cerebellum, each adult Purkinje cell is innervated by a single climbing fiber (see Chapter 18); however, during early development, each Purkinje cell receives multiple climbing fiber inputs. Finally, in the visual cortex, initial binocular innervation of cells is eliminated to establish segregated molecularly driven inputs (see Chapter 23). The pattern of synaptic connections that emerges in the adult is not simply a consequence of the biochemical identities of synaptic partners or other determinate developmental rules. Rather, the mature wiring plan is the result of a much more flexible process in which neuronal connections are formed, removed, and remodeled according to local circumstances that reflect molecular constraints as well as ongoing electrical activity. These interactions guarantee that every target cell is innervated—and continues to be innervated—by the right number of inputs and synapses, and that every innervating axon contacts the right number of target cells with an appropriate number of synaptic endings. Thus, the regulation of **convergence** (the number of inputs to a target cell) and **divergence** (the number of connections made by a neuron) in the developing nervous system is another key consequence of trophic interactions among neurons and their targets. The regulation of convergence and divergence by neurotrophic interactions is also importantly influenced by the form of neurons, particularly the elaboration of dendrites (Box C), a feature that is also subject to neurotrophic control (see below).

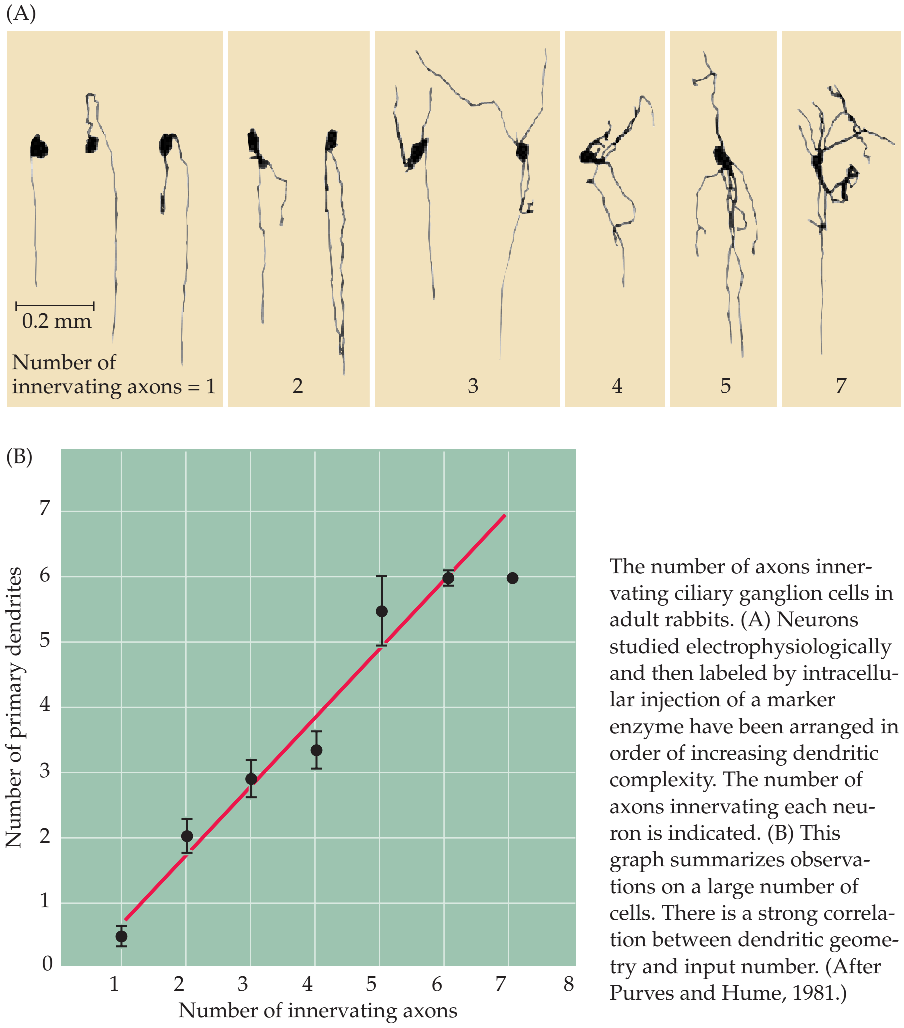
Thus, trophic interactions regulate three essential steps in the formation of mature neural circuits: matching numbers of afferents to the available target space; regulating the degree of innervation of individual afferents and their postsynaptic partners, and modulating the growth and shape of axonal and dendritic branches.

Molecular Basis of Trophic Interactions

The three major functions of neurotrophic signaling—survival of a subset of neurons from a considerably larger population, subsequent formation and maintenance of appropriate numbers of connections, and the elaboration of axonal and dendritic branches to support these connections—can be rationalized in part by the supply and availability of trophic factors. These rules entail several general assumptions about neurons and their targets (which may be other neurons, muscles, or other peripheral structures). First, neurons depend on the availability of some minimum amount of trophic factor for survival, and subsequently for the persistence of appropriate numbers of target connections. Second, target tissues synthesize and make available to developing neurons appropriate trophic factors. Third, targets produce trophic factors in limited amounts; in consequence, the survival of developing neurons (and later, the persistence of neuronal connections and growth and further differentiation of neurons) depends on neuronal competition for

Box C
Why Do Neurons Have Dendrites?

Perhaps the most striking feature of neurons is their diverse morphology. Some classes of neurons have no dendrites at all; others have a modest dendritic arborization; still others have an arborization that rivals the complex branching of a fully mature tree (see Figures 1.2 and 1.6). Why should this be? Although there are many reasons for this diversity, neuronal geometry influences the number of different inputs that a target neuron receives by modulating competitive interactions among the innervating axons.



The number of axons innervating ciliary ganglion cells in adult rabbits. (A) Neurons studied electrophysiologically and then labeled by intracellular injection of a marker enzyme have been arranged in order of increasing dendritic complexity. The number of axons innervating each neuron is indicated. (B) This graph summarizes observations on a large number of cells. There is a strong correlation between dendritic geometry and input number. (After Purves and Hume, 1981.)

Evidence that the number of inputs a neuron receives depends on its geometry has come from studies of the peripheral autonomic system, where it is possible to stimulate the full complement of axons innervating an autonomic ganglion and its constituent neurons. This approach is not usually feasible in the central nervous system because of the anatomical complexity of most central circuits. Since individual postsynaptic neurons can also be labeled via an intracellular recording electrode, electrophysiological measurements of the number of different axons innervating a neuron can routinely be correlated with target cell shape. In both parasympathetic and sympathetic ganglia, the degree of preganglionic convergence onto a neuron is proportional to its dendritic complexity. Thus, neurons that lack dendrites altogether are generally innervated by a single input, whereas neurons with increasingly complex dendritic arborizations are innervated by a proportionally greater number of different axons (see figure). This correlation of neuronal geometry and input number holds within a single ganglion, among different ganglia in a single species, and among homologous ganglia across a range of species. Since ganglion cells that have few or no dendrites are initially innervated by several different inputs (see text), confining inputs to the limited arena of the developing cell soma evidently enhances competition between them, whereas the addition of dendrites to a neuron allows multiple inputs to persist in peaceful coexistence. Importantly, the dendritic complexity of at least some classes of autonomic ganglion cells is influenced by neurotrophins.

A neuron innervated by a single axon will clearly be more limited in the scope of its responses than a neuron innervated by 100,000 inputs (1 to 100,000 is the approximate range of convergence in the mammalian brain). By regulating the number of inputs that neurons receive, dendritic form greatly influences function.

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the available factor. One much-studied trophic molecule, the protein called nerve growth factor (NGF), has provided support for these assumptions. Although the story of nerve growth factor certainly does not explain all aspects of trophic interactions, it has been a useful paradigm for understanding in more detail the manner in which neural targets influence the survival and connections of the nerve cells that innervate them.

NGF was discovered in the early 1950s by Rita Levi-Montalcini and Viktor Hamburger at Washington University. On the basis of experiments involving the survival of motor neurons after removal of developing limb buds (see Figure 22.9), they made an informed guess that the target tissues provided some sort of signal to the relevant neurons, and that limited amounts of this agent explained the apparently competitive nature of nerve cell death. Accordingly, Levi-Montalcini and Hamburger undertook a series of experiments to explore the source and nature of the postulated signal, focusing on dorsal root and sympathetic ganglion neurons rather than the spinal cord neurons. A former student of Hamburger's had earlier removed a limb from a chick embryo and replaced it with a piece of mouse tumor. The surprising outcome of this experiment was that the tumor apparently furnished an even more potent stimulus than the limb, causing an enlargement of the sensory and sympathetic ganglia that normally innervate the appendage. In further experiments, Levi-Montalcini and Hamburger provided evidence that the tumor (a mouse sarcoma) secreted a soluble factor that stimulated the survival and growth of both sensory and sympathetic ganglion cells. Levi-Montalcini then devised a bioassay for the presumed agent and, in collaboration with Stanley Cohen, isolated and characterized the molecule—which had by then been named nerve growth factor for its ability to induce the massive outgrowth of neurites from explanted ganglia (Figure 22.12). (The term "neurite" is used to describe neuronal branches when it is not known whether they are axons or dendrites.) NGF was identified as a protein and was substantially purified from a rich biological source, the salivary glands of the male mouse. Subsequently, its amino acid sequence and 3 dimensional structure was determined and the cDNAs encoding NGF cloned in several species.

Support for the idea that NGF is important for neuronal survival in more physiological circumstances emerged from a number of further observations. Depriving developing mice of NGF by the chronic administration of an NGF antiserum or other strategies resulted in adult mice lacking most NGF-dependent neurons (Figure 22.12). Conversely, injection of exogenous NGF into newborn rodents caused enlargement of sympathetic ganglia, an effect opposite that of NGF deprivation. Neurons in ganglia in treated animals were both more numerous and larger; there was also more neuropil between cell bodies, suggesting an overgrowth of axons, dendrites, and other cellular elements. The dramatic influence of NGF on cell survival, together with what was known about the significance of neuronal death in development, suggested that NGF is indeed a target-derived signal that serves to match the number of nerve cells to the number of target cells.

The ability of NGF to support neuronal survival (and of NGF deprivation to enhance cell death) is not in itself unassailable proof of a physiological role for this factor in development. In particular, these observations provided no direct evidence for NGF synthesis by (and uptake from) neuronal targets. This gap was filled by another series of ingenious experiments in several laboratories that showed NGF to be present in sympathetic targets, and to be quantitatively correlated with the density of sympathetic innervation. Furthermore, messenger RNA for NGF was demonstrated in targets innervated

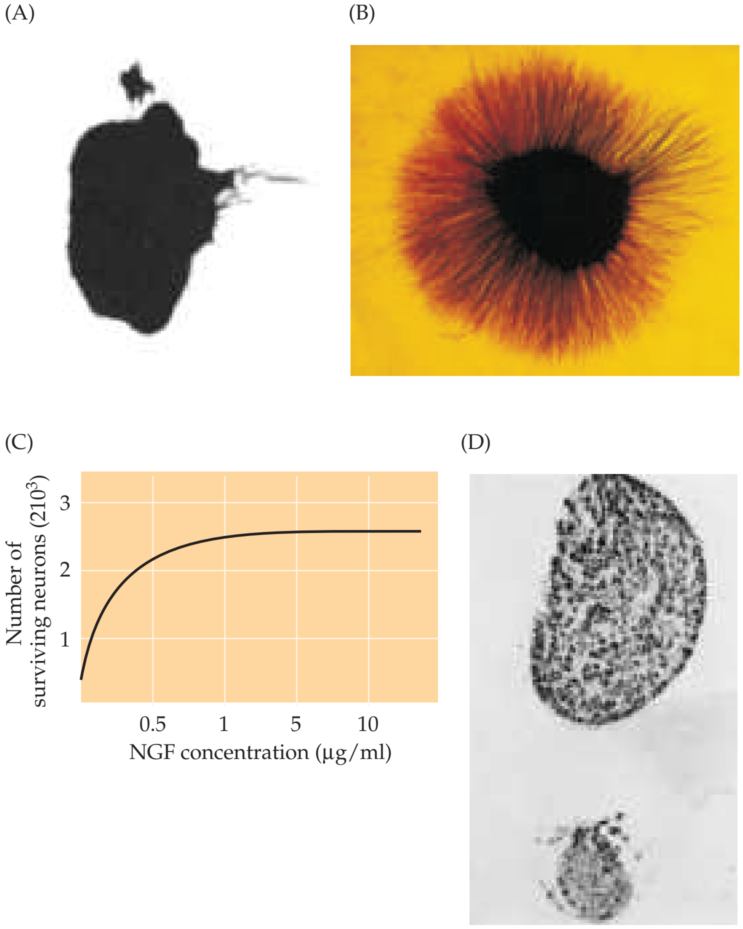
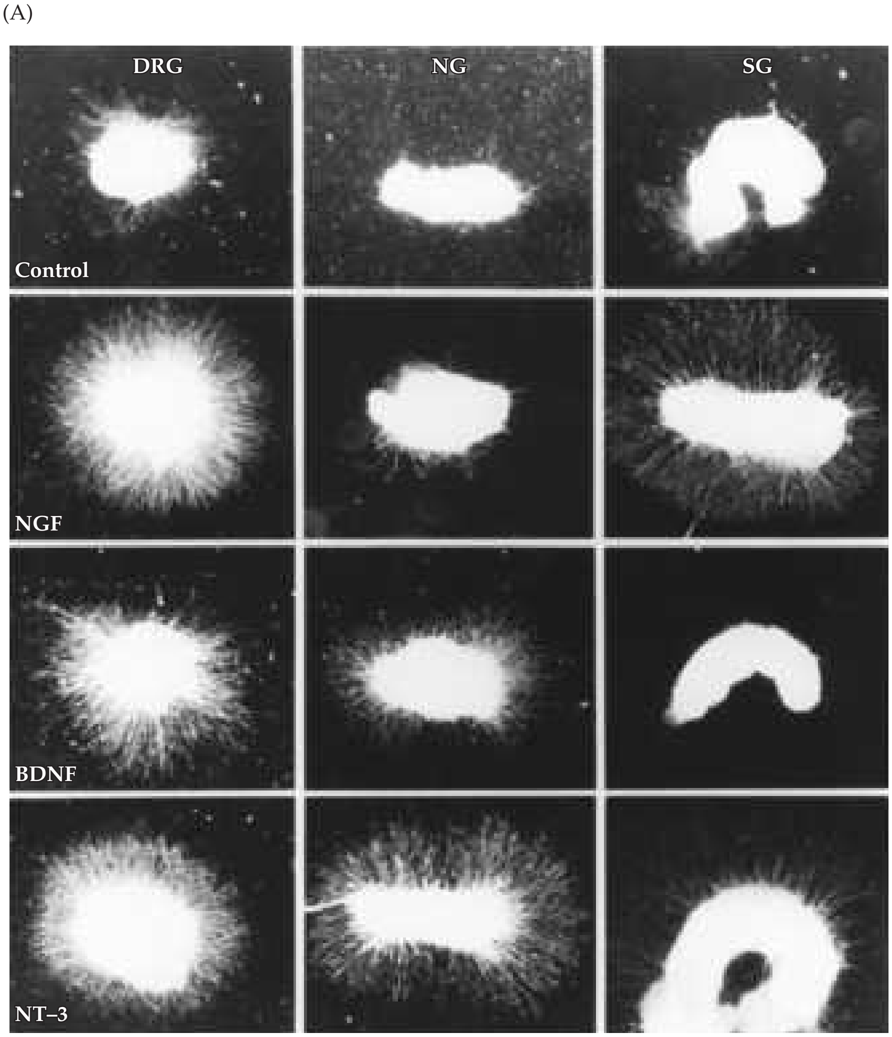

(A)
(B)
(C)
(D)
Number of surviving neurons (210^3)
3
2
1
0.5
1
5
10
NGF concentration (µg/ml)

Figure 22.12 Effect of NGF on the outgrowth of neurites. (A) A chick sensory ganglion taken from an 8-day-old embryo and grown in organ culture for 24 hours in the absence of NGF. Few, if any, neuronal branches grow out into the plasma clot in which the explant is embedded. (B) A similar ganglion in identical culture conditions 24 hours after the addition of NGF to the medium. NGF stimulates a halo of neurite outgrowth from the ganglion cells. (C, D) Effect of NGF on the survival of sympathetic ganglion cells. (C) The survival of newborn rat sympathetic ganglion cells grown in culture for 30 days evaluated quantitatively as a function of NGF concentration. Dose-response curves such as this one confirm the strict dependence of these neurons on the availability of NGF. (D) Cross section of a superior cervical ganglion from a normal 9-day-old mouse (top) compared to a similar section from a littermate injected daily since birth with NGF antiserum (bottom). The ganglion of the treated mouse shows marked atrophy, with obvious loss of nerve cells. (A, B from Purves and Lichtman, 1985, courtesy of R. Levi-Montalcini; C after Chun and Patterson, 1977; D from Levi-Montalcini, 1972.)

by sympathetic and sensory ganglia, but not in the ganglia themselves or in targets innervated by other types of nerve cells. As might be expected from such specificity, the NGF-sensitive neurons were also shown to have receptor molecules for the trophic factor (see next section). Importantly, the NGF message appears only after ingrowing axons have reached their targets; this fact makes it unlikely that secreted NGF acts in vivo as a chemotropic (guidance) molecule (like netrins and other cell adhesion molecules discussed earlier). Finally, the great majority of sympathetic neurons are lacking in mice in which the gene encoding NGF has been deleted.

In sum, several decades of work in a number of laboratories have shown that NGF mediates cell survival among two specific neuronal populations in birds and mammals (sympathetic neurons and a subpopulation of sensory ganglion cells). These observations include the death of the relevant neurons in the absence of NGF; the survival of a surplus of neurons in the presence of augmented levels of the factor; the presence and production of NGF in neuronal targets; and the existence of receptors for NGF in innervating nerve terminals. Indeed, these observations define the criteria that must be satisfied in order to conclude that a given molecule is indeed a neurotrophic factor.

Although NGF remains the most thoroughly studied neurotrophic factor, it was apparent from the outset that only certain classes of nerve cells respond to NGF. Work from a number of laboratories in the late 1980’s and early 1990’s has shown that NGF is only one member of a family of related trophic molecules, the **neurotrophins**. At present, there are three well-char-



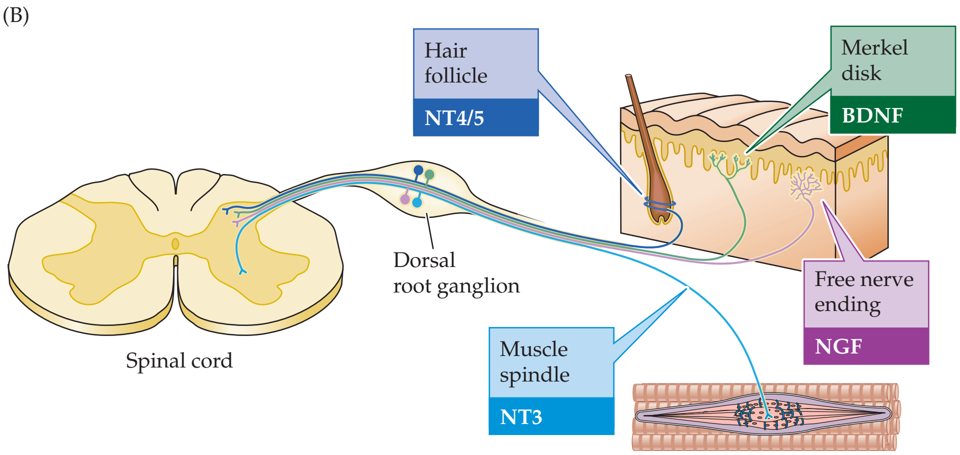


Figure 22.13 The influence of neurotrophins. (A) Effect of NGF, BDNF, and NT-3 on the outgrowth of neurites from explanted, dorsal root ganglia (left column), nodose ganglia (middle column), and sympathetic ganglia (right column). The specificities of these several neurotrophins are evident in the ability of NGF to induce neurite outgrowth from sympathetic and dorsal root ganglia, but not from nodose ganglia (which are cranial nerve sensor ganglia that have a different embryological origin from dorsal root ganglia); of BDNF to induce neurite outgrowth from dorsal root and nodose ganglia, but not from sympathetic ganglia; and of NT-3 to induce neurite outgrowth from all three types of ganglia. (B) Specific influence of neurotrophins in vivo. Distinct classes of peripheral somatosensory receptors and the dorsal root ganglion cells that give rise to these sensory endings depend on different trophic factors in specific target tissues. (A from Maisonpierre et al., 1990; B after Bibel and Barde, 2000.)

acterized members of the neurotrophin family in addition to NGF: **brain-derived neurotrophic factor** (**BDNF**), **neurotrophin-3** (**NT-3**), and **neurotrophin 4/5 (NT-4/5)** (Box D). Although several neurotrophins are homologous in amino acid sequence and structure, they are very different in their specificity (Figure 22.13). For example, NGF supports the survival of (and neurite outgrowth from) sympathetic neurons, while another family member—BDNF—cannot. Conversely, BDNF, but not NGF, can support the sur-

Box D

The Discovery of BDNF and the Neurotrophin Family

During the 30 years or so that work with NGF showed it to fulfill all the criteria for a target-derived neurotrophic factor (see text), it became clear that NGF affected only a few specific populations of peripheral neurons. It was therefore presumed that other neurotrophic factors must exist that followed similar rules, but supported the survival and growth of other classes of neurons. In particular, whereas NGF was shown to be secreted by the *peripheral* targets of primary sensory and sympathetic neurons, other factors were presumably produced by target neurons in the brain and spinal cord that supported the *central* projections of sensory neurons.

The serendipity of the mouse salivary gland and its extraordinary levels of NGF was not repeated for these additional factors, however, and the hunt for the neurotrophic factors presumed to act in the central nervous system proved to be a long and arduous one. Indeed, it was not until the 1980s that the pioneering work of Yves Barde, Hans Thoenen, and their colleagues succeeded in identifying and purifying a factor from the brain that they named brain-derived neurotrophic factor (BDNF). As with NGF, this factor was purified on the basis of its ability to promote the survival and neurite outgrowth of sensory neurons. However, BDNF is expressed at such vanishingly small levels that over a million-fold purification was necessary before the protein could be identified!

Thereafter, microsequencing and recombinant DNA technology allowed rapid progress even from the scant amounts of purified BDNF protein that were available. By 1989, Barde's group had succeeded in cloning the cDNA for BDNF. Surprisingly—despite its entirely different origin and distinct neuronal specificity—BDNF turned out to be a close relative of NGF. Based on the homologies between the primary structures of NGF and BDNF, the following year six independent laboratories (including Barde's) reported the cloning of a third member of the neurotrophin family, neurotrophin-3 (NT-3). At present, four members of the neurotrophin family have been reported in a variety of vertebrate species (see text).

Experiments on BDNF and other members of the neurotrophin family over last decade have supported the conclusion that the survival and growth of different neuronal populations in both the PNS and CNS is dependent on different neurotrophins, relationships that are mediated by expression of membrane receptors that are specific for each neurotrophin (see figure). However, the dramatic relationship between the survival of neuronal populations and neurotrophins has not been found in the CNS, where BDNF, NT-3, and NT-4/5, as well as their receptors, are primarily expressed. The most striking demonstration of this difference has been in "knockout" mice in which individual genes encoding neurotrophins or Trk receptors have been deleted: While these genetic deletions have led to predictable deficits in the PNS (see text), they have generally had minimal impact on CNS structure and function.

Thus, the part played by neurotrophins in the CNS remains much less certain. One possibility is that these neurotrophins are more involved in regulating neuronal differentiation and phenotype in the CNS than in supporting neuronal survival per se. In this regard, the expression of neurotrophins is tightly regulated by electrical and synaptic activity, suggesting that they may also influence experience-dependent processes during the formation of circuits in the CNS.

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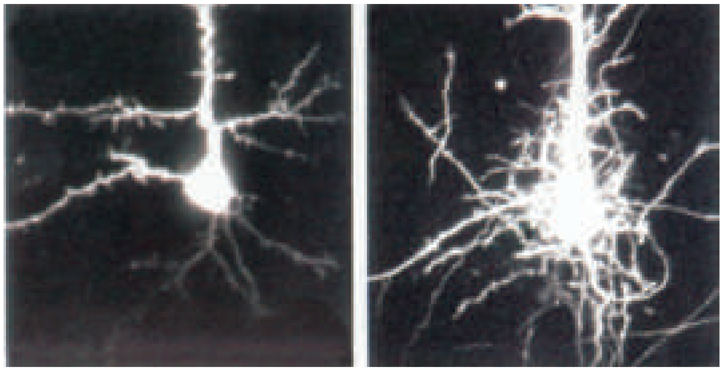

Neurotrophins influence dendritic arbors in the developing cerebral cortex. The cell on the left was transfected with the gene for green fluorescent protein (GFP) alone, the one on the right with GFP plus the gene encoding BDNF. Within a day, BDNF-transfected neurons grow elaborate dendritic branches, reminiscent of the NGF-induced halo in peripheral ganglia (see Figure 22.12B). (From Horch et al., 1999.)

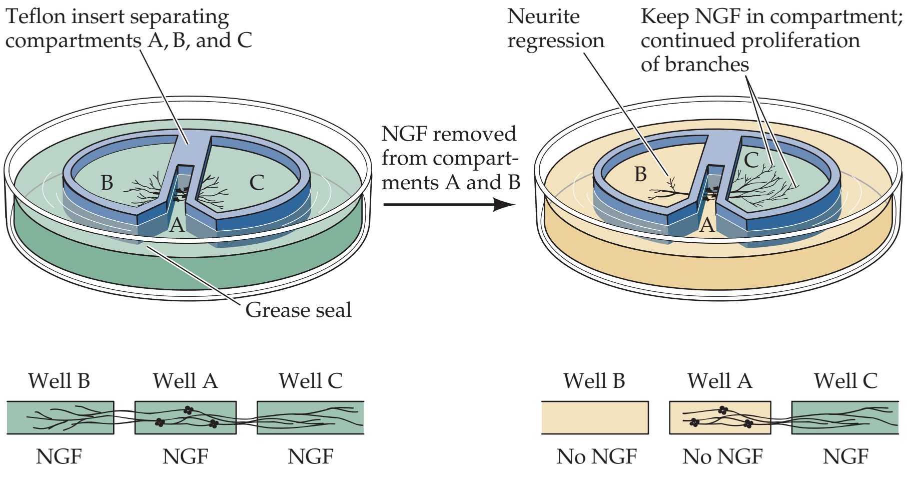
Teflon insert separating compartments A, B, and C
B
C
A
Grease seal
NGF removed from compartments A and B
Neurite regression
Keep NGF in compartment; continued proliferation of branches
B
C
A
Well B
Well A
Well C
NGF
NGF
NGF
Well B
Well A
Well C
No NGF
No NGF
NGF

Figure 22.14 Evidence that NGF can influence neurite growth by local action. Three compartments of a culture dish (A, B, C) are separated from one another by a plastic divider sealed to the bottom of the dish with grease. Isolated rat sympathetic ganglion cells plated in compartment A can grow through the grease seal and into compartments B and C. (A magnified view looking down on the compartments is shown below.) Growth into a lateral chamber occurs as long as the compartment contains an adequate concentration of NGF. Subsequent removal of NGF from a compartment causes a local regression of neurites without affecting the survival of cells or neurites in the other compartments. These observations show that neuritic growth can be locally controlled by neurotrophins. (After Campenot, 1981.)

vival of certain sensory ganglion neurons, which have a different embryonic origin. NT-3 supports both of these populations. Given the diverse systems whose growth and connectivity must be coordinated during neural development, this specificity makes good sense.

Neurotrophin Signaling

All of the biological observations on neurotrophic interactions suggest that signaling via the neurotrophins will activate at least 3 different kinds of responses: cell survival/death, synapse stabilization/elimination, and process growth/retraction. This impression was initially generated by experiments that presented NGF to subsets of neural processes without exposing the cell body to the factor (Figure 22.14). The result of this experiment indicated that NGF could act locally to stimulate neurite growth—even while other processes of the same cell, deprived of NGF, are retracting. In addition, physiological experiments indicated that NGF and other neurotrophins could influence synaptic activity and plasticity, again independent of their effects on cell survival. Thus, there is a high degree of selectivity of neurotrophin actions, depending on the neurotrophic factor available, the stage of differentiation of the responding neuron as well as the cellular domains where neurotrophic signaling takes place.

The selective actions of the neurotrophins arise from their interactions with two classes of receptors: the Trk (for tyrosine kinase) receptors and the p75 receptor. There are three Trk receptors, each of which is a single transmembrane protein with a cytoplasmic tyrosine kinase domain. **TrkA** is primarily a receptor for NGF, **TrkB** a receptor for BDNF and NT-4/5, and **TrkC** a receptor for NT-3 (Figure 22.15). In addition, all neurotrophins can activate the **p75** receptor protein. The interactions between neurotrophins and p75 demonstrate another level of selectivity and specificity of neurotrophin signaling. All neurotrophins are secreted in an unprocessed form that undergoes subsequent proteolytic cleavage. The p75 receptor has high affinity for unprocessed neurotrophins, and low affinity for the processed ligands, while the Trk receptors have high affinity for processed ligands only. The expression of a particular Trk receptor subtype or p75 therefore confers the capacity to respond to the corresponding neurotrophin. Since neurotrophins, Trk

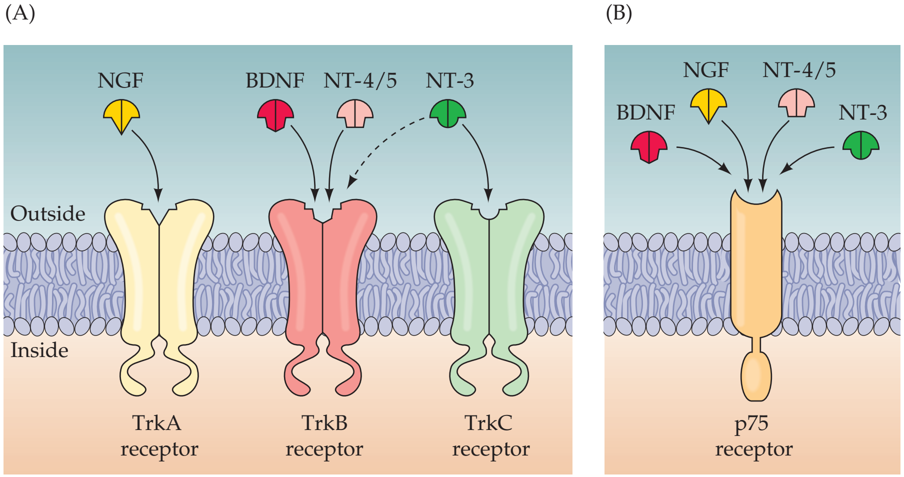

Figure 22.15 Neurotrophin receptors and their specificity for the neurotrophins. (A) The Trk family of receptor tyrosine kinases for the neurotrophins. TrkA is primarily a receptor for NGF, TrkB a receptor for BDNF and NT-4/5, and TrkC a receptor for NT-3. Because of the high degree of structural homology among both the neurotrophins and the Trk receptors, there is some degree of cross-activation between factors and receptors. For example, NT-3 can bind to and activate TrkB under some conditions, as indicated by the dashed arrow. These distinct receptors allow various neurons to respond selectively to the different neurotrophins. (B) The p75 low-affinity neurotrophin receptor binds all neurotrophins at low affinities (as its name implies). This receptor confers the ability to respond to a broad range of neurotrophins upon fairly broadly distributed classes of neurons in the peripheral and central nervous systems.

receptors and p75 are expressed only in subsets of neurons, the selective binding between ligand and receptor accounts for the specificity of the relevant neurotrophic interactions.

Signaling via either the Trk receptors or the p75 receptor can lead to changes in the three domains that are sensitive to neurotrophic signaling: cell survival/death, cell and process growth/differentiation, and activity dependent synaptic stabilization or elimination. Each receptor class (Trk or p75) can engage distinct intracellular signaling cascades that lead to changes in cell state (motility, adhesion, etc.) or gene expression and thus result in the known consequences of neurotrophic interactions (Figure 22.16). Thus, understanding the specific effects of neurotrophic interactions for any cell relies on at least three pieces of information: the neurotrophins locally available, the combination of receptors on the relevant neuron, and the intracellular signaling pathways expressed by that neuron. The subtlety and diversity of neuronal circuits is thus set during development by different combinations of neurotrophins, their receptors, and signal transduction mechanisms that in concert determine the numbers of neurons, their shape, and their patterns of connections. Presumably, disruption of these neurotrophin-dependent processes, either during development or in the adult brain, can result in neurodegenerative conditions in which neurons die due to lack of appropriate trophic support, with devastating consequences for the circuits that the cells define, and the behaviors that are controlled by those circuits. Indeed, the pathogenic mechanisms of neurodegenerative diseases as diverse as amyotrophic lateral sclerosis (ALS), Parkinson's, Huntington's, and Alzheimer's diseases may all reflect deficiencies of neurotrophic regulation.

Summary

Neurons in the developing brain must integrate a variety of molecular signals in order to determine where to send their axons, whether to live or die, what cells to form synapses on, how many synapses to make, and whether

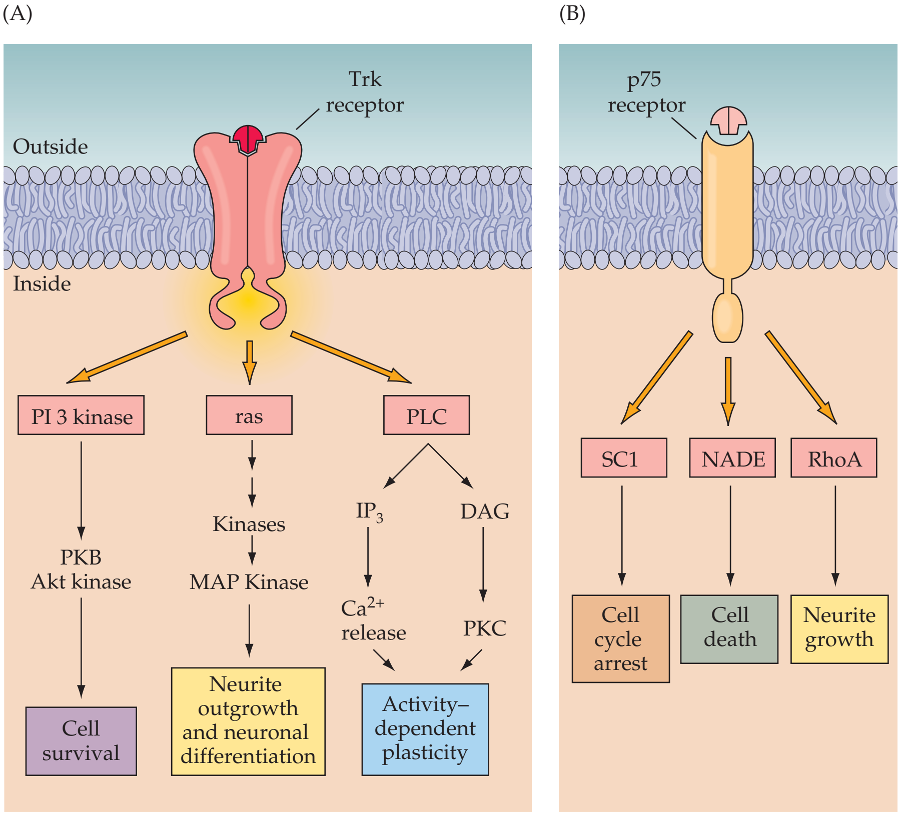
(A)
Trk receptor
Outside
Inside
PI 3 kinase
ras
PLC
IP3
DAG
Kinases
PKB
Akt kinase
MAP Kinase
Ca2+ release
PKC
Cell survival
Neurite outgrowth and neuronal differentiation
Activity–dependent plasticity
(B)
p75 receptor
SC1
NADE
RhoA
Cell cycle arrest
Cell death
Neurite growth

Figure 22.16 Signaling through the neurotrophins and their receptors. (A) Signaling via Trk dimers can lead to a variety of cellular responses, depending on the intracellular signaling cascade engaged by the receptor after binding to the ligand. The possibilities include cell survival (via the protein kinase C/AKT pathway); neurite growth (via the MAP-Kinase pathway); and activity-dependent plasticity (via the Ca^{2+}/calmodulin and PKC pathways). (B) Signaling via the p75 pathway can lead to neurite growth via interaction with Rho kinases, or cell cycle arrest and cell death via other distinct intracellular signaling cascades.

to retain them. Fixed and/or diffusible adhesive, chemotropic, chemorepulsive, and trophic molecules all regulate the trajectory of growing axons and the synaptic connections they make with target cells. These developmental interactions occur over weeks, months, and to some extent may continue at a low level over the entire lifetime of the animal—as body size and functional demands change. Cell adhesion molecules influence the initial targeting of axons to appropriate target zones by modulating the direction and extent of growth cone motility. The earliest effects of trophic agents are on cell survival and differentiation. Once the appropriate number of neurons is established, trophic signals continue to govern the establishment of neural connections, particularly the extent of axonal and dendritic arborizations. Defects in the early guidance of axons are responsible for a variety of congenital neurological syndromes, and conditions thought to reflect trophic dysfunction may underlie degenerative diseases such as amyotrophic lateral sclerosis and Parkinson's disease. Understanding the molecular basis of axon guidance, synapse formation, and trophic signaling began a century ago and has now burgeoned into a broad effort that continues to identify additional factors and signaling pathways to illuminate their varied roles in both the developing and adult brain. A further goal that now seems within reach is the application of this knowledge to understanding a spectrum of previously intractable neurological diseases.

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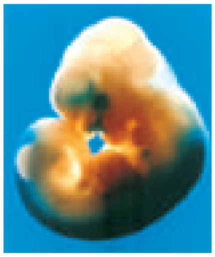
Chapter 23



Modification of Brain Circuits as a Result of Experience

Overview

The rich diversity of human personalities, abilities, and behavior is undoubtedly generated by the uniqueness of individual human brains. These fascinating neurobiological differences among humans derive from both genetic and environmental influences. The first steps in the construction of the brain's circuitry—the establishment of distinct brain regions, the generation of neurons, the formation of major axon tracts, the guidance of growing axons to appropriate targets, and the initiation of synaptogenesis—rely largely on the intrinsic cellular and molecular processes described in the previous chapters. Once the basic patterns of brain connections are established, however, patterns of neuronal activity (including those that are elicited by experience) modify the synaptic circuitry of the developing brain. Neuronal activity generated by interactions with the outside world in postnatal life thus provides a mechanism by which the environment can influence brain structure and function. Many of the effects of activity are transduced via signaling pathways that modify levels of intracellular Ca^{2+} and thus influence local cytoskeletal organization as well as gene expression (see Chapter 7). This activity-mediated influence on the developing brain is most consequential during temporal windows called critical periods. As humans and other mammals mature, the brain becomes increasingly refractory to the lessons of experience, and the cellular mechanisms that modify neural connectivity become less effective.

Critical Periods

The cellular and molecular mechanisms outlined in Chapters 21 and 22 construct a nervous system of impressive anatomical complexity. These mechanisms and their developmental consequences are sufficient to create some remarkably sophisticated innate or "instinctual" behaviors (see Box A in Chapter 30). For most animals, the behavioral repertoire, including foraging, fighting, and mating strategies, largely relies on patterns of connectivity established by intrinsic developmental mechanisms. However, the nervous systems of complex ("higher") animals, including humans, clearly adapt to and are influenced by the particular circumstances of an individual's environment. These environmental factors are especially influential in early life, during temporal windows called **critical periods**. In some cases, such as the acquisition of language, instructive influences from the environment are obviously required for the normal development of the behavior (i.e., exposure to the individual's native language). Moreover, some behaviors, such as imprinting in birds (Box A), are expressed only if animals have certain spe-

Box A

Built-In Behaviors

The idea that animals already possess a set of behaviors appropriate for a world not yet experienced has always been difficult to accept. However, the preeminence of instinctual responses is obvious to any biologist who looks at what animals actually do. Perhaps the most thoroughly studied examples occur in young birds. Hatchlings emerge from the egg with an elaborate set of innate behaviors. First, of course, is the complex behavior that allows the chick to escape from the egg. Having emerged, a variety of additional abilities indicate how much early behavior is "preprogrammed" (see Box A in Chapter 30).

In a series of seminal observations, Konrad Lorenz, working with geese, showed that goslings follow the first large, moving object that they see and hear during their first day of life. Although this object is normally the mother goose, Lorenz found that goslings can imprint on a wide range of animate and inanimate objects presented during this period, including Lorenz himself (see figure). The window for imprinting in goslings is less than a day: If animals are not exposed to an appropriate stimulus during this time, they will never form the appropriate parental relationship. Once imprinting occurs, however, it is irreversible, and geese will continue to follow inappropriate objects (male conspecifics, people, or even inanimate objects). In many mammals, auditory and visual systems are poorly developed at birth, and maternal imprinting relies on olfactory and/or gustatory cues. For example, during the first week of life (but not later), infant rats develop a lifelong preference to odors associated with their mother's nipples. As in birds, this variety of filial imprinting also plays a role in their social development and later sexual preferences.

Imprinting is a two-way street, with parents (especially mothers) rapidly forming exclusive bonds with their offspring. This phenomenon is especially important in animals like sheep that live in large groups or herds and produce offspring at about the same time of year. Ewes have a critical period 2–4 hours after giving birth during which they imprint on the scent of their own lamb. Following this time, they rebuff approaches by other lambs.

The relevance of this work to primates was underscored in the 1950s by Harry Harlow and his colleagues at the University of Wisconsin. Harlow isolated monkeys within a few hours of birth and raised them in the absence of either a natural mother or a human substitute. In the best-known of these experiments, the baby monkeys had one of two maternal surrogates: a "mother" constructed of a wooden frame covered with wire mesh that supported a nursing bottle, or a similarly shaped object covered with terrycloth. When presented with this choice, the baby monkeys preferred the terrycloth mother and spent much of their time clinging to it, even if the feeding bottle was with the wire mother. Harlow took this to mean that newborn monkeys have a built-in need for maternal care and have at least some innate idea of what a mother should be like. More recently, a number of other endogenous behaviors have been carefully studied in infant monkeys, including a naïve monkey's fear reaction to the presentation of certain objects (e.g., a snake) and the "looming" response (fear elicited by the rapid approach of any formidable object). Most of these built-in behaviors have analogs in human infants.

Konrad Lorenz, followed by imprinted geese. (Photograph courtesy of H. Kacher.)

Taken together, these observations make plain that many complicated behaviors, emotional responses, and other predilections are well established in the nervous system prior to any significant experience, and that the need for certain kinds of early experience for normal development is predetermined. These built-in behaviors and their neural substrates have presumably evolved to give newborns a better chance of surviving in a predictably dangerous world.

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cific experiences during a sharply restricted time in early postnatal (or posthatching; see Box A) development. On the other hand, critical periods for sensory and motor skills, or complex behaviors such as human language, are longer and much less well delimited.

Despite the fact that critical periods vary widely in both the behaviors affected and their duration, they all share some basic properties. A critical period is defined as the time during which a given behavior is especially susceptible to, and indeed requires, specific environmental influences to develop normally. Once this period ends, the behavior is largely unaffected by subsequent experience (or even by the complete absence of the relevant experience). Conversely, failure to be exposed to appropriate stimuli during the critical period is difficult or in some cases impossible to remedy subsequently.

While psychologists and ethologists (biologists who study the natural behavior of animals) have long recognized that early postnatal or posthatching life is a period of special sensitivity to environmental influences, their studies of critical periods focused on behavior. Work in the last few decades has increasingly examined the underlying changes in the relevant brain circuits and their mechanisms.

The Development of Language: Example of a Human Critical Period

Many animals communicate by means of sound, and some (humans and songbirds are examples) learn these vocalizations. There are, in fact, provocative similarities in the development of human language and birdsong (Box B). Many other animal vocalizations, like alarm calls in mammals and birds, are innate, and require no experience to be correctly produced. For example, quail raised in isolation or deafened at birth so that they never hear conspecifics nonetheless produce the full repertoire of species-specific vocalizations. In contrast, humans obviously require extensive postnatal experience to produce and decode speech sounds that are the basis of language. The various forms of early language exposure, including the "baby talk" that parents and other adults often use to communicate with children as they begin to acquire language may actually serve to emphasize important perceptual distinctions that facilitate proper language production and comprehension.

Importantly, this linguistic experience, to be effective, must occur in early life. The requirement for perceiving and practicing language during a critical period is apparent in studies of language acquisition in congenitally deaf children. Whereas most babies begin producing speechlike sounds at about 7 months (babbling), congenitally deaf infants show obvious deficits in their early vocalizations, and such individuals fail to develop language if not provided with an alternative form of symbolic expression (such as sign language; see Chapter 26). If, however, these deaf children are exposed to sign language at an early age (from approximately six months onward), they begin to "babble" with their hands just as a hearing infant babbles audibly. This suggests that, regardless of the modality, early experience shapes language behavior (Figure 23.1). Children who have acquired speech but subsequently lose their hearing before puberty also suffer a substantial decline in spoken language, presumably because they are unable to hear themselves talk and thus lose the opportunity to refine their speech by auditory feedback during the final stages of the critical period for language.

Examples of pathological situations in which normal children were never exposed to a significant amount of language make the same point. In one

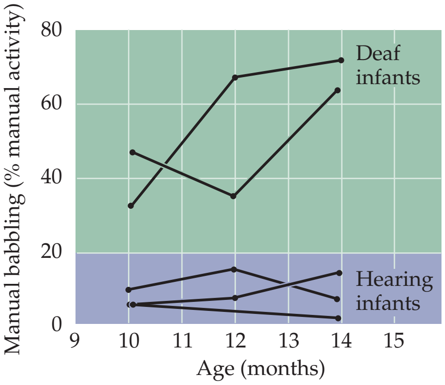


Figure 23.1 Manual "babbling" in two deaf infants raised by deaf, signing parents compared to manual babble in three hearing infants. Babbling was judged by scoring hand positions and shapes that showed some resemblance to the components of American Sign Language. In deaf infants, meaningful hand shapes increase as a percentage of manual activity between ages 10 and 14 months. Hearing children raised by hearing, speaking parents do not produce similar hand shapes. (After Petito and Marentette, 1991.)

Box B

Birdsong

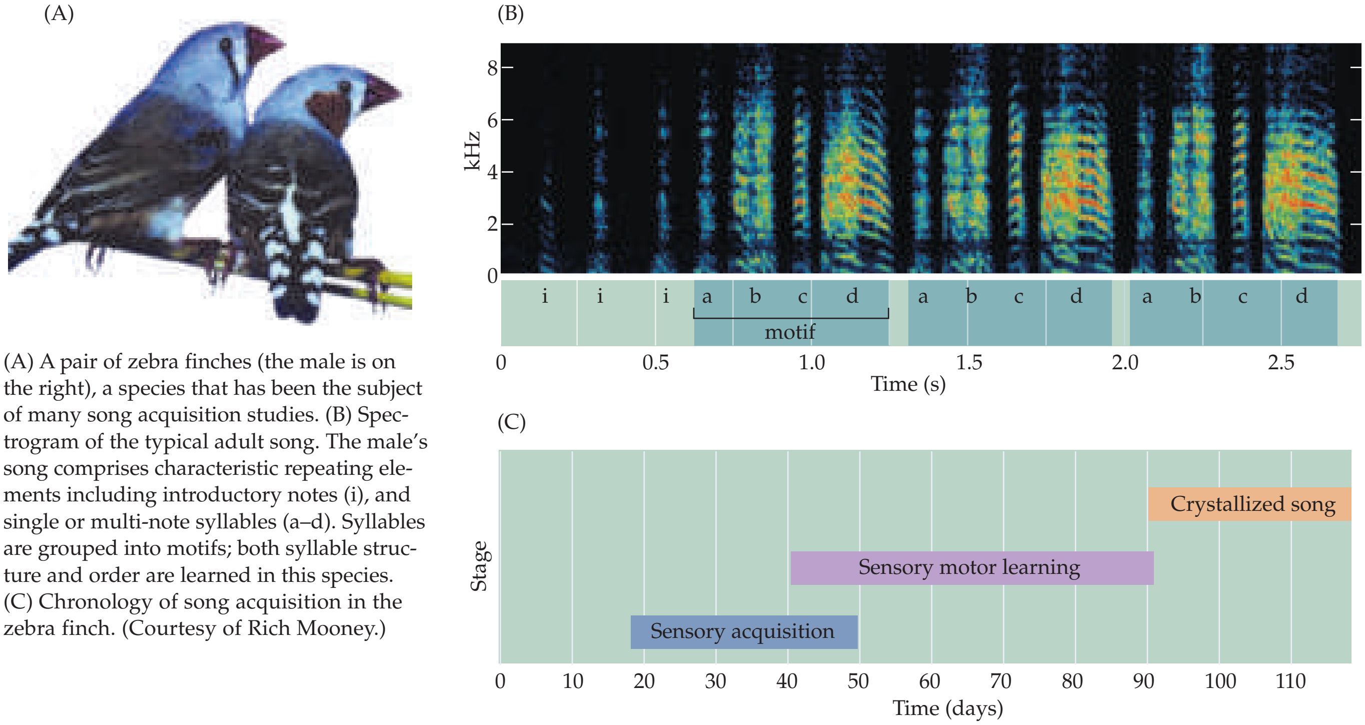
Anyone witnessing language development in a child cannot help but be amazed at how quickly learning takes place. This facility contrasts with the adult acquisition of a new language, which can be a painfully slow process that never produces complete fluency. In fact, many learned behaviors are acquired during a period in early life when experience exerts an especially potent influence on subsequent behavior. Particularly well characterized is the sensitive period for learning courtship songs by oscine songbirds such as canaries and finches. In these species, the quality of early sensory exposure is the major determinant of subsequent perceptual and behavioral capabilities. Furthermore, developmental periods for learning these and other behaviors are restricted during postnatal life, suggesting that the nervous system changes in some manner to become refractory to further experience. Understanding how critical periods are regulated has many implications, not least the possibility of reactivating this enhanced learning capacity in adults. Nonetheless, such periods are often highly specialized for the acquisition of species-typical behaviors and are not merely times of general enhanced learning.

Avian song learning illustrates the interactions between intrinsic and environmental factors in this developmental process. Many birds sing to attract mates, but oscine songbirds are special in that their courtship songs are dependent on auditory and vocal experience. The sensitive period for song learning comprises an initial stage of sensory acquisition, when the juvenile bird listens to and memorizes the song of a nearby adult male tutor (usually of its own species), and a subsequent stage of vocal learning, when the young bird matches its own song to the now-memorized tutor model via auditory feedback. This sensory motor learning stage ends with the onset of sexual maturity, when songs become acoustically stable, or crystallized. In all species studied to date, young songbirds are especially impressionable during the first two months after hatching and then become refractory to further exposure to tutor song as they age. The impact of this early experience is profound, and the memory it generates can remain intact for months, and perhaps years, before the onset of the vocal practice phase. Even constant exposure to other songs after sensory acquisition during the sensitive period ends does not affect this memory: The songs heard during sensory acquisition, but not later, are those that the bird vocally mimics. Early auditory experience is crucial to the bird's Darwinian success. In the absence of a tutor, or if raised only in the presence of another species, birds produce highly abnormal "isolate" songs, or songs of the foster species, neither of which succeeds in attracting females of their own kind.

Two other features of song learning indicate an intrinsic predisposition for this specialized form of vocal learning. First, juveniles often need to hear the tutor song only 10 or 20 times to then vocally mimic it many months later. Second, when presented with a variety of songs played from tape recordings that include their own and other species' songs, juvenile birds preferentially copy the song of their own species, even with no external reinforcement. These observations show that juveniles are not really

well-documented case, a girl was raised by deranged parents until the age of 13 under conditions of almost total language deprivation. Despite intense subsequent training, she never learned more than a rudimentary level of communication. This and other examples of so-called "feral children" starkly define the importance of early experience for language development as well as other aspects of social communication and personality. In contrast to the devastating effects of deprivation on children, adults retain their ability to speak and comprehend language even if decades pass without exposure to human communication (a fictional example would be Robinson Crusoe). In short, the normal acquisition of human speech is subject to a critical period: The process is sensitive to experience or deprivation during a restricted period of life (before puberty) and is relatively refractory to similar experience or deprivations in adulthood.

On a more subtle level, the phonetic structure of the language an individual hears during early life shapes both the perception and production of speech. Many of the thousands of human languages and dialects use appre-



(A) A pair of zebra finches (the male is on the right), a species that has been the subject of many song acquisition studies. (B) Spectrogram of the typical adult song. The male's song comprises characteristic repeating elements including introductory notes (i), and single or multi-note syllables (a–d). Syllables are grouped into motifs; both syllable structure and order are learned in this species. (C) Chronology of song acquisition in the zebra finch. (Courtesy of Rich Mooney.)

"naïve," but are innately biased to learn the songs of their own species over those of others. In short, intrinsic factors make the nervous system of oscine birds especially sensitive to songs that are species-typical. It is likely that similar biases influence human language learning.

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ciably different speech elements (called phonemes) to produce spoken words (examples are the phonemes *ba* and *pa* in English; see Chapter 26). Very young human infants can perceive and discriminate between differences in *all* human speech sounds, and are not innately biased towards phonemes characteristic of any particular language. However, this universal perceptual capacity does not persist. For example, adult Japanese speakers cannot reliably distinguish between the *r* and *l* sounds in English, presumably because this phonemic distinction is not made in Japanese and thus not reinforced by experience during the critical period. Nonetheless, 4-month-old Japanese infants can make this discrimination as reliably as 4-month-olds raised in English-speaking households (as indicated by increased suckling frequency or head turning in the presence of a novel stimulus). By 6 months of age, however, infants begin to show preferences for phonemes in their native language over those in foreign languages, and by the end of their first year no longer respond robustly to phonetic elements peculiar to non-native languages. The ability to perceive these

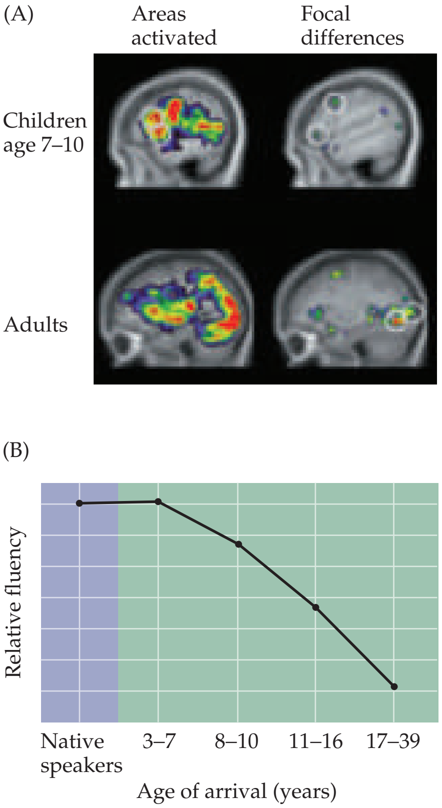

Figure 23.2 Learning language. (A) Maps derived from fMRI in adults and children performing visual word processing tasks. Images are sagittal sections with the front of the brain toward the left. The top row shows the range of active areas (left) and foci of activity based on group averages (right) for children ages 7–10. The bottom row shows analogous results for adults performing the same task. (B) A critical period for learning language is shown by the decline in language ability (fluency) of non-native speakers of English as a function of their age upon arrival in the United States. The ability to score well on tests of English grammar and vocabulary declines from approximately age 7 onward. (A after Schlaggar et. al., 2002; B after Johnson and Newport, 1989.)

phonemic contrasts, when attended to, evidently persists for several more years, as evidenced by the fact that children can learn to speak a second language without accent and with fluent grammar until about age 7 or 8. After this age, however, performance gradually declines no matter what the extent of practice or exposure (Figure 23.2).

A number of changes in the developing brain could explain these observations. One possibility is that experience acts selectively to preserve the circuits in the brain that perceive phonemes and phonetic distinctions. The absence of exposure to non-native phonemes would then result in a gradual atrophy of the connections representing those sounds, accompanied by a declining ability to distinguish between them. In this formulation, circuits that are used are retained, whereas those that are unused get weaker (and presumably disappear). Alternatively, experience could promote the growth of rudimentary circuitry pertinent to the experienced sounds. Recent comparisons of patterns of activity in children (age 7–10) and adults performing very specific word processing tasks suggest that different brain regions are activated for the same task in children and adults. While the significance of such differences is not clear—they may reflect anatomical plasticity associated with critical periods, or distinct modes of performing language tasks in children versus adults—there is nevertheless an indication that brain circuits change to accommodate language function during early life.

Critical Periods in Visual System Development

Although critical periods for language and other distinctively human behaviors are in some ways the most compelling examples of this phenomenon, it is difficult if not impossible to study the underlying changes in the human brain. A much clearer understanding of how changes in connectivity might contribute to critical periods has come from studies of the developing visual system in experimental animals with highly developed visual abilities—particularly cats and monkeys. In an extraordinarily influential series of experiments, David Hubel and Torsten Wiesel found that depriving animals of normal visual experience during a restricted period of early postnatal life irreversibly alters neuronal connections (and functions) in the visual cortex. These observations provided the first evidence that the brain translates the effects of early experience (that is, patterns of neural activity) into more or less permanently altered wiring.

To understand these experiments and their implications, it is important to review the organization and development of the mammalian visual system. Recall that information from the two eyes is first integrated in the primary visual (striate) cortex, where most afferents from the lateral geniculate nucleus of the thalamus terminate (see Chapter 11). In some mammals—carnivores, anthropoid primates, and humans—the afferent terminals form an alternating series of eye-specific domains in cortical layer IV called **ocular dominance columns** (Figure 23.3). As already described in Chapter 11, ocular dominance columns can be visualized by injecting tracers, such as radioactive proline, into one eye; the tracer is then transported along the visual pathway to specifically label the geniculocortical terminals (i.e., synaptic terminals in the visual cortex) corresponding to that eye (Figure 23.3, Box C). In the adult macaque monkey, the domains representing the two eyes are stripes of about equal width (0.5 mm) that occupy roughly equal areas of layer IV of the primary visual cortex. Electrical recordings confirm that the cells within layer IV of macaques respond strongly or exclusively to stimulation of either the left or the right eye, while neurons in layers above

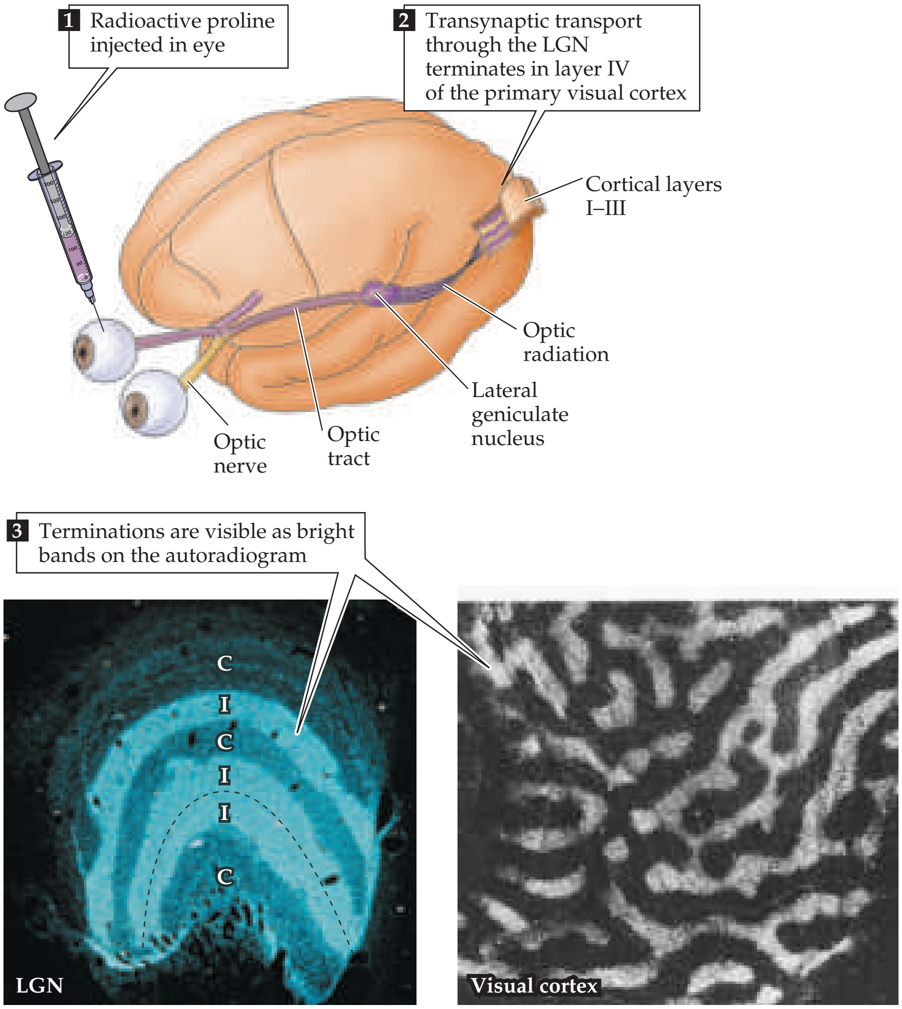
1 Radioactive proline injected in eye
2 Transynaptic transport through the LGN terminates in layer IV of the primary visual cortex
Cortical layers I–III
Optic radiation
Lateral geniculate nucleus
Optic tract
Optic nerve
3 Terminations are visible as bright bands on the autoradiogram
C
I
C
I
I
C
LGN
Visual cortex

Figure 23.3 Ocular dominance columns (which in most anthropoid primates are really stripes or bands) in layer IV of the primary visual cortex of an adult macaque monkey. Diagram indicates the labeling procedure (see also Box C); following transynaptic transport, the pattern of geniculocortical terminations related to that eye is visible as a series of bright stripes in this autoradiogram of a section through layer IV in the plane of the cortex (that is, as if looking down on the cortical surface). The dark areas are the zones occupied by geniculocortical terminals related to the other eye. The pattern of human ocular dominance columns is shown in Figure 12.10. (From LeVay, Wiesel, and Hubel, 1980.)

and below layer IV integrate inputs from the left and right eyes and respond to visual stimuli presented to either eye. Ocular dominance is thus apparent in two related phenomena: the degree to which individual cortical neurons are driven by stimulation of one eye or the other, and domains (stripes) in cortical layer IV in which the majority of neurons are driven exclusively by one eye or the other. The clarity of these patterns of connectivity and the precision by which experience via the two eyes can be manipulated led to the series of experiments described in the following section that greatly clarified the neurobiological processes underlying critical periods.

Effects of Visual Deprivation on Ocular Dominance

As described in Chapter 11, if an electrode is passed at a shallow angle through the cortex while the responses of individual neurons to stimulation of one or the other eye are being recorded, detailed assessment of ocular dominance can be made at the level of individual cells (see Figure 11.13). In their original studies, Hubel and Wiesel assigned neurons to one of seven ocular dominance categories, and this classification scheme has become standard in the field. Group 1 cells were defined as being driven only by stimulation of the contralateral eye; group 7 cells were driven entirely by the

Box C

Transneuronal Labeling with Radioactive Amino Acids

Unlike many brain structures, ocular dominance columns are not easily visible by means of conventional histology. Thus, the striking cortical patterns evident in cats and monkeys were not seen until the early 1970s, when the technique of anterograde tracing using radioactive amino acids was introduced. In this approach, an amino acid commonly found in proteins (usually proline) is radioactively tagged and injected into the area of interest. Neurons in the vicinity take up the label from the extracellular space and incorporate it into newly made proteins. Some of these proteins are involved in the maintenance and function of the neuron's synaptic terminals; thus, they are shipped via anterograde transport from the cell body to nerve terminals, where they accumulate. After a suitable interval, the tissue is fixed, and sections are made, placed on glass slides, and coated with a sensitive photographic emulsion. The radioactive decay of the labeled amino acids in the proteins causes silver grains to form in the emulsion. After several months of exposure, a heavy concentration of silver grains accumulates over the regions that contain synapses originating from the injected site. For example, injections into the eye will heavily label the terminal fields of retinal ganglion cells in the lateral geniculate nucleus.

Transneuronal transport takes this process a step further. After tagged proteins reach the axon terminals, a fraction is actually released into the extracellular space, where the proteins are degraded into amino acids or small peptides that retain their radioactivity. An even smaller fraction of this pool of labeled amino acids is taken up by the postsynaptic neurons, incorporated again into proteins, and transported to synaptic terminals of the second set of neurons. Because the label passes from the presynaptic terminals of one set of cells to the postsynaptic target cells, the process is called transneuronal transport. By such transneuronal labeling, the chain of connections originating from a particular structure can be visualized. In the case of the visual system, proline injections into one eye label appropriate layers of the lateral geniculate nucleus (as well as other retinal ganglion cell targets such as the superior colliculus), and subsequently the terminals in the visual cortex of the geniculate neurons receiving inputs from that eye. Thus, when sections of the visual cortex are viewed with dark-field illumination to make the silver grains glow a brilliant white against the unlabeled background, ocular dominance columns in layer IV are easily seen (see Figure 23.3).

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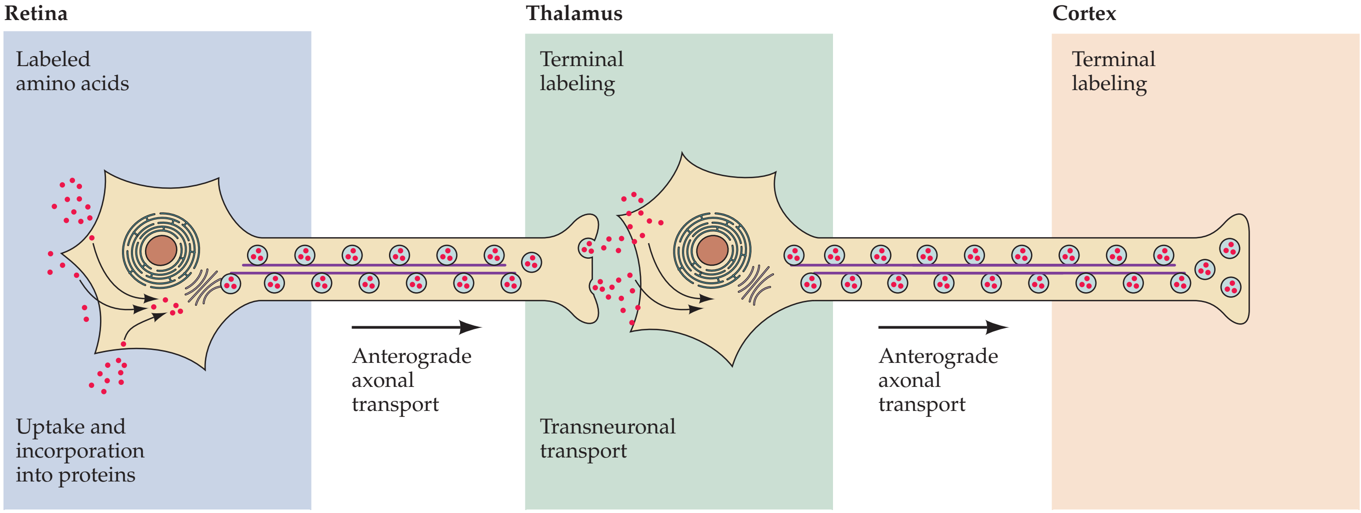
Transneuronal transport. A neuron in the retina is shown taking up a radioactive amino acid, incorporating it into proteins, and moving the proteins down the axons and across the extracellular space between neurons. This process is repeated in the thalamus, and eventually label accumulates in the thalamocortical terminals in layer IV of the primary visual cortex.



ipsilateral eye. Neurons driven equally well by either eye were assigned to group 4. Using this approach, they found that the ocular dominance distribution across the cortical layers in primary visual cortex is roughly Gaussian in a normal adult (cats were used in these experiments). Most cells were activated to some degree by both eyes, and about a quarter were more activated by either the contralateral or ipsilateral eye (Figure 23.4A).

Hubel and Wiesel then asked whether this normal distribution of ocular dominance could be altered by visual experience. When they simply closed one eye of a kitten early in life and let the animal mature to adulthood (which takes about 6 months), a remarkable change was observed. Electrophysiological recordings now showed that very few cortical cells could be driven from the deprived eye; that is, the ocular dominance distribution had shifted such that nearly all cells were driven by the eye that had remained

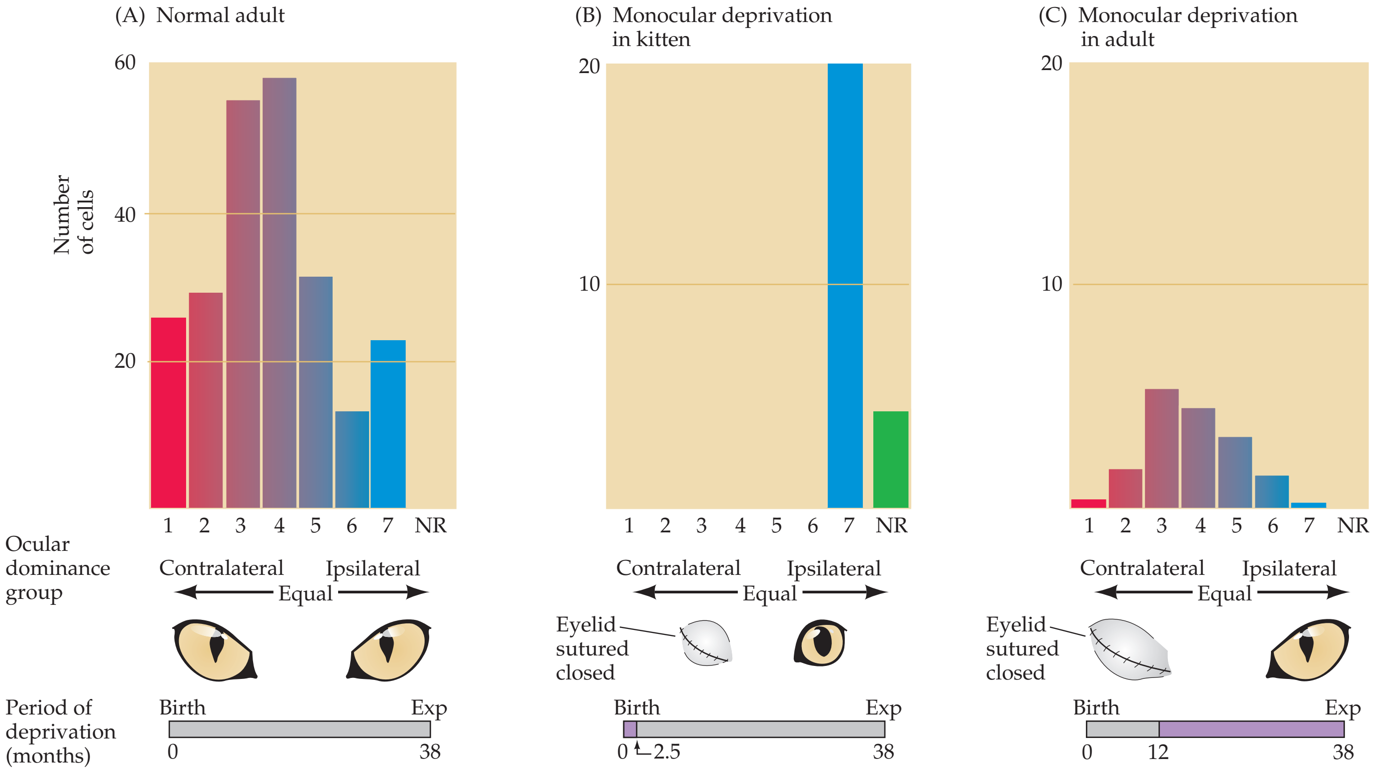


Figure 23.4 Effect of early closure of one eye on the distribution of cortical neurons driven by stimulation of both eyes. (A) Ocular dominance distribution of single unit recordings from a large number of neurons in the primary visual cortex of normal adult cats. Cells in group 1 were activated exclusively by the contralateral eye, cells in group 7 by the ipsilateral eye. Diagrams below these graphs indicate procedure, and bars indicate duration of deprivation (purple). "Exp" = time at which experimental observations were made. (B) Following closure of one eye from 1 week after birth until 2.5 months of age (indicated by the bar underneath the graph), no cells could be activated by the deprived (contralateral) eye. Some cells could not be activated by either eye (NR). Note that the closed eye is opened at the time of the experimental observations, and that the recordings are not restricted to any particular cortical layer. (C) A much longer period of monocular deprivation in an adult cat has little effect on ocular dominance (although overall cortical activity is diminished). In this case, the contralateral eye was closed from 12 to 38 months of age. (A after Hubel and Wiesel, 1962; B after Wiesel and Hubel, 1963; C after Hubel and Wiesel, 1970.)

open (Figure 23.4B). Recordings from the retina and lateral geniculate layers related to the deprived eye indicated that these more peripheral stations in the visual pathway worked quite normally. Thus, the absence of cortical cells that responded to stimulation of the closed eye was not a result of retinal degeneration or a loss of retinal connections to the thalamus. Rather, the deprived eye had been functionally disconnected from the visual cortex. Consequently, such animals are behaviorally blind in the deprived eye. This "cortical blindness," or amblyopia, is permanent (see next section). Even if the formerly deprived eye is subsequently left open indefinitely, little or no recovery occurs.

Remarkably, the same manipulation—closing one eye—had no effect on the responses of cells in the visual cortex of an adult cat (Figure 23.4C). If one eye of a mature cat was closed for a year or more, both the ocular dominance distribution measured across all cortical layers and the animal's visual behavior were indistinguishable from normal when tested through the reopened eye. Thus, sometime between the time a kitten's eyes open (about a week after birth) and a year of age, visual experience determines how the visual cortex is wired with respect to eye dominance. After this time, deprivation or manipulation has little or no permanent, detectable effect. In fact, further experiments showed that eye closure is effective only if the deprivation occurs during the first 3 months of life. In keeping with the ethological observations described earlier in the chapter, Hubel and Wiesel called this period of susceptibility to visual deprivation the critical period for the development of ocular dominance. During the height of the critical period (about 4 weeks of age in the cat), as little as 3 to 4 days of eye closure profoundly alters the ocular dominance profile of the striate cortex (Figure 23.5). Similar experiments in the monkey have shown that the same phenomenon occurs in primates, although the critical period is longer (up to about 6 months of age).

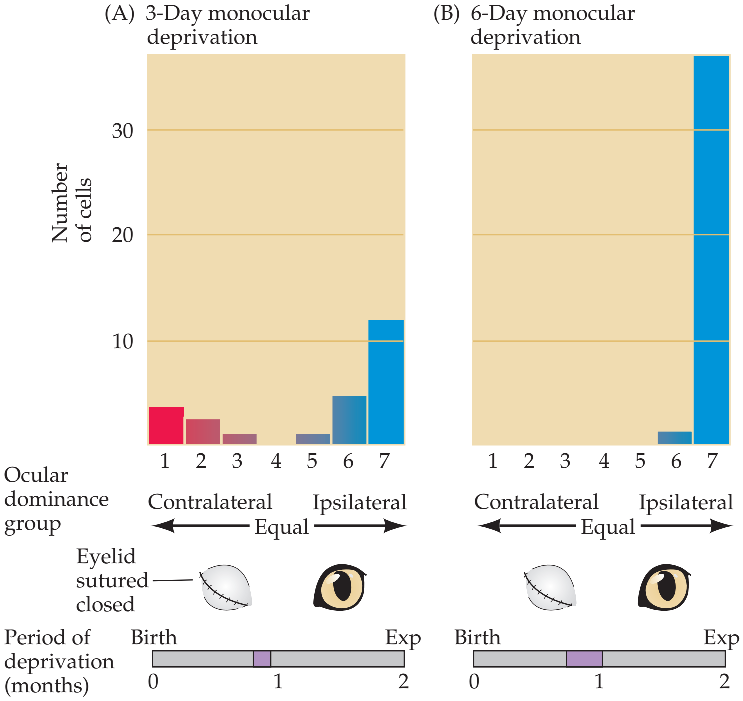


Figure 23.5 The consequences of a short period of monocular deprivation at the height of the critical period in the cat. Just 3 days of deprivation in this example (A) produced a significant shift of cortical innervation in favor of the non-deprived eye; 6 days of deprivation (B) produced an almost a compete shift. Bars below each histogram indicate the period of deprivation, as in Figure 23.4. (After Hubel and Wiesel, 1970.)

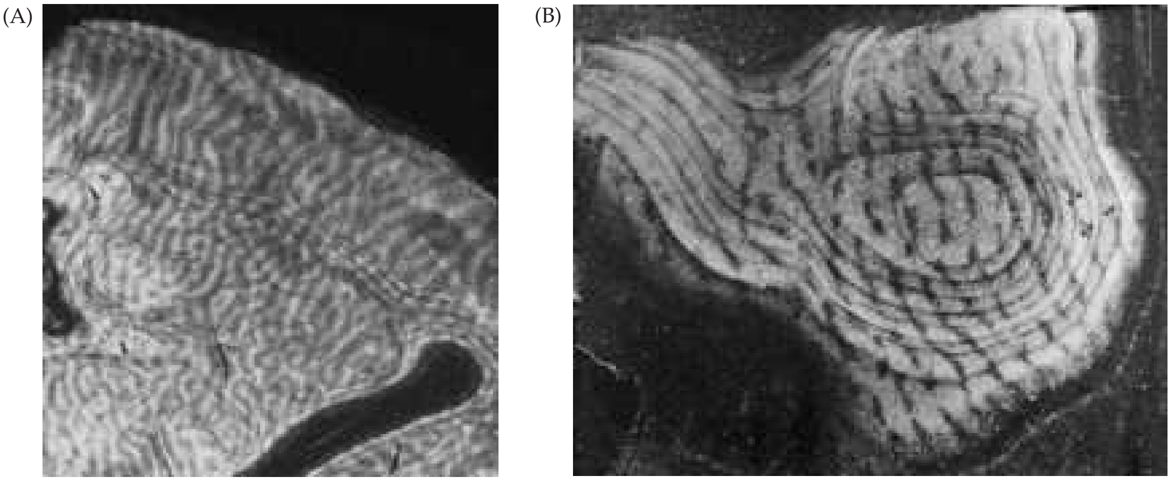


Figure 23.6 Effect of monocular deprivation on ocular dominance columns in the macaque monkey. (A) In normal monkeys, ocular dominance columns seen as alternating stripes of roughly equal width are already present at birth. (B) The picture is quite different after monocular deprivation. This dark-field autoradiograph shows a reconstruction of several sections through layer IV of the primary visual cortex of a monkey whose right eye was sutured shut from 2 weeks of age to 18 months, when the animal was sacrificed. Two weeks before death, the normal (left) eye was injected with radiolabeled amino acids (see Box C). The columns related to the nondeprived eye (white stripes) are much wider than normal, whereas as those related to the deprived eye are shrunken. (A from Horton and Hocking, 1999; B from Hubel et al., 1977.)

Thus the key advance arising from Hubel and Wiesel's early work was to show that visual deprivation causes changes in cortical connectivity that influence the functional response properties of individual neurons (Figure 23.6). The implications of altered cortical circuitry as a result of experience was amply confirmed by subsequent anatomical studies. In monkeys, the alternating stripelike patterns of geniculocortical axon terminals in layer IV representing the two eyes that define ocular dominance columns—is already present at birth (Figure 23.6A). Thus, the visual cortex is clearly not a blank slate on which the effects of experience are later inscribed. Nevertheless, animals deprived of vision in one eye from birth develop abnormal patterns of ocular dominance stripes in the visual cortex (Figure 23.6B). The stripes related to the open eye are substantially wider than normal, whereas the stripes representing the deprived eye are correspondingly diminished. The absence of cortical neurons that respond to the deprived eye in electrophysiological studies is not simply a result of the relatively inactive inputs withering away. If this were the case, one would expect to see areas of layer IV devoid of any thalamic innervation. Instead, inputs from the active (open) eye take over some of the territory that formerly belonged to the inactive (closed) eye.

Hubel and Wiesel interpreted these results as demonstrating a competitive interaction between the two eyes during the critical period (see Chapter 22).In summary, the cortical representation of both eyes starts out equal, and in a normal animal, this balance is retained if both eyes experience roughly comparable levels of visual stimulation. When, however, an imbalance in visual experience is induced by monocular deprivation, the active eye gains a competitive advantage and replaces many of the synaptic inputs from the closed eye, such that few if any neurons can be driven by the deprived eye (see Figure 22.4B). These observations in experimental animals have important implications for children with birth defects or ocular injuries that cause an imbalance of inputs from the two eyes. Unless the imbalance is corrected during the critical period, the child may ultimately have poor binocular fusion, diminished depth perception, and degraded acuity; in other words, the child's vision may be permanently impaired (see the next section).

The idea that a competitive imbalance underlies the altered distribution of inputs after deprivation has been confirmed by closing *both* eyes shortly after birth, thereby equally depriving all visual cortical neurons of normal experience during the critical period. The arrangement of ocular dominance recorded some months later is, by either electrophysiological or anatomical criteria, much closer to normal than if just one eye is closed. Although several peculiarities in the response properties of cortical cells are apparent, roughly normal proportions of neurons representing the two eyes are present. Because there is no imbalance in the visual activity of the two eyes (both sets of related cortical inputs being deprived), both eyes retain their territory in the cortex. If disuse atrophy of the closed-eye inputs were the main effect of deprivation, then binocular deprivation during the critical period would cause the visual cortex to be largely unresponsive.

Experiments using techniques that label individual axons from the lateral geniculate nucleus terminating in layer IV have shown in greater detail what happens to the arborizations of individual neurons after visual deprivation (Figure 23.7). As noted, monocular deprivation causes a loss of cortical territory related to the deprived eye, with a concomitant expansion of the open eye's territory. At the level of single axons, these changes are reflected in an increased extent and complexity of the arborizations related to the open eye, and a decrease in the size and complexity of the arborizations related to the deprived eye. Individual neuronal arborizations can be substantially altered after as little as one week of deprivation, and perhaps even less. This latter finding highlights the ability of developing thalamic and cortical neurons to rapidly remodel their connections—presumably making and breaking synapses—in response to environmental circumstances.

Visual Deprivation and Amblyopia in Humans

These developmental phenomena in the visual system of experimental animals accord with clinical problems in children who have experienced similar deprivation. The loss of acuity, diminished stereopsis, and problems with fusion that arise from early deficiencies of visual experience is called **amblyopia** (from the Greek meaning "dim sight").

In humans, amblyopia is most often the result of **strabismus**—a misalignment of the two eyes due to improper control of the direction of gaze by the eye muscles and referred to colloquially as "lazy eye." Depending on the muscles affected, the misalignment can produce convergent strabismus,

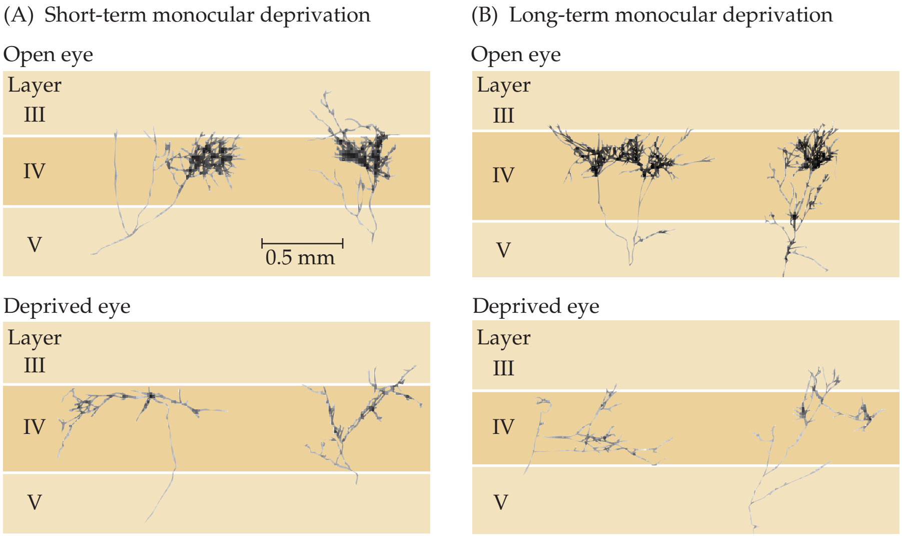


Figure 23.7 Terminal arborizations of lateral geniculate nucleus axons in the visual cortex can change rapidly in response to monocular deprivation during the critical period. (A) After only a week of monocular deprivation, axons from the deprived eye have greatly reduced numbers of branches compared with those from the open eye. (B) Deprivation for longer periods does not result in appreciably larger changes. Numbers on the left of each figure indicate cortical layers. (After Antonini and Stryker, 1993.)

called **esotropia** ("cross-eyed"), or divergent strabismus, called **exotropia**. These alignment errors are surprisingly common, affecting about 5% of children. Since such misalignments produce double vision, the response of the visual system in some of these individuals is to suppress input from one eye by mechanisms that are not completely understood, but are thought to reflect competitive interactions during the critical period. Functionally, however, the suppressed eye eventually comes to have very low acuity and may render the affected individual effectively blind in that eye. Thus, early surgical correction of ocular misalignment (by adjusting lengths of extraocular muscles) has become an essential treatment for strabmismic children. Another cause of visual deprivation in humans is cataracts. Cataracts, which can be caused by several congenital conditions, render the lens opaque. Diseases such as onchocerciasis ("river blindness," a parasitic infection caused by the nematode *Onchocerca volvulus*) and trachoma (caused by *Chlamydia trachomatis,* a small, bacteria-like organism) affect millions of people in undeveloped tropical regions, often inducing corneal opacity in one or both eyes. A cataract in one eye is functionally equivalent to monocular deprivation in experimental animals; left untreated in children, this defect also results in an irreversible effect on the visual acuity of the deprived eye. If either the cataract or corneal opacity is removed before about 4 months of age, however, the consequences of monocular deprivation are largely avoided. As expected from Hubel and Wiesel's work, bilateral cataracts, which are similar to binocular deprivation in experimental animals, produce less dramatic deficits even if treatment is delayed. Apparently, unequal competition during the critical period for normal vision (e.g., that caused by monocular deprivation) is more deleterious than the complete abrogation of visual input that occurs with binocular deprivation.

In keeping with the findings in experimental animals, the visual abilities of individuals monocularly deprived of vision as adults (by cataracts or corneal scarring, for example) are much less affected, even after decades, when vision is restored (although there may be important psychological consequences of restoring sight after prolonged binocular blindness, as has been engagingly described by the neurologist Oliver Sacks among others). Nor is there any evidence of anatomical change in this circumstance. For instance, a patient whose eye was surgically removed in adulthood showed normal ocular dominance columns when his brain was examined postmortem many years later (see Figure 11.10). Thus, one can detect evidence of critical period phenomena for visual cortical development and behavior in the visual system of humans based upon careful examination of patients with opthalmic disease or other lesions.

Mechanisms by which Neuronal Activity Affects the Development of Neural Circuits

How, then, are differences in patterns of neural activity translated into changes in neural circuitry? In 1949, the psychologist D. O. Hebb hypothesized that coordinated activity of a presynaptic terminal and a postsynaptic neuron strengthens the synaptic connection between them. Hebb's postulate, as it has come to be known, was originally formulated to explain the cellular basis of learning and memory (see Chapter 24), but this general concept has been widely applied to situations that involve long-term modifications in synaptic strength, including those that occur during development of neural circuits. In this context, Hebb's postulate implies that synaptic terminals strengthened by correlated activity will be retained or sprout new branches,

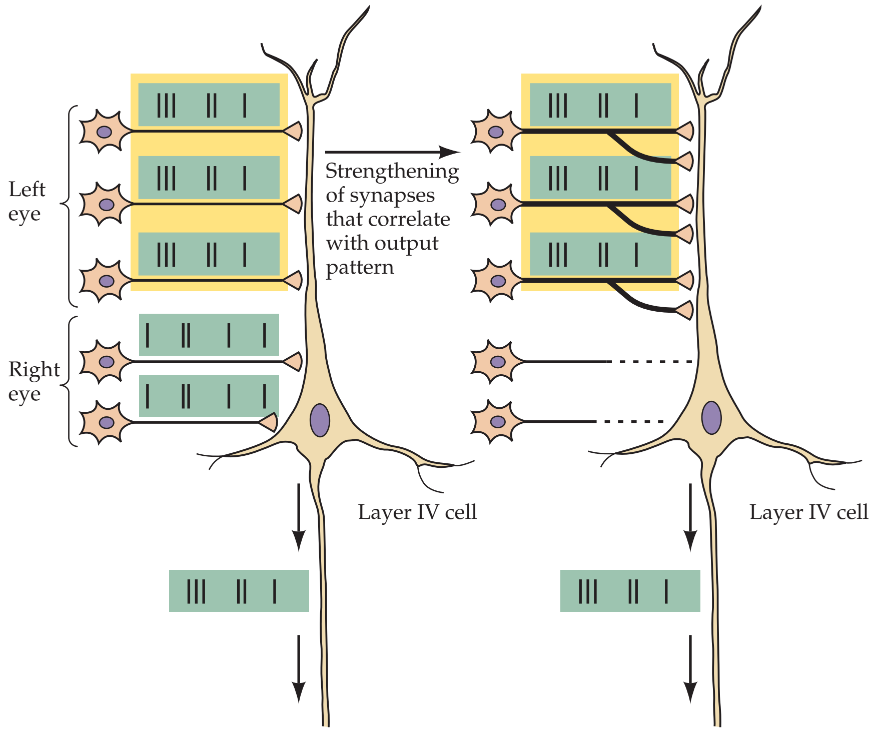

Left eye
Right eye
Strengthening of synapses that correlate with output pattern
Layer IV cell
Layer IV cell

Figure 23.8 Representation of Hebb's postulate as it might operate during development of the visual system. The cell represents a postsynaptic neuron in layer IV of the primary visual cortex. Early in development, inputs from the two eyes converge on single postsynaptic cells. The two sets of presynaptic inputs, however, have different patterns of electrical activity (represented by the short vertical bars). In the example here, the three left eye inputs are better able to activate the postsynaptic cell; as a result, their activity is highly correlated with the postsynaptic cell's activity. According to Hebb's postulate, these synapses are therefore strengthened. The inputs from the right eye carry a different pattern of activity that is less well correlated with the majority of the activity elicited in the postsynaptic cell. These synapses gradually weaken and are eventually eliminated (right-hand side of figure), while the correlated inputs form additional synapses.

whereas those that are persistently weakened by uncorrelated activity will eventually lose their hold on the postsynaptic cell (Figure 23.8; see also Chapter 22). In the visual system, the action potentials of the thalamocortical inputs related to one eye are presumably better correlated with each other than with the activity related to the other eye—at least in layer IV. If sets of correlated inputs tend to dominate the activity of groups of locally connected postsynaptic cells, this relationship would exclude uncorrelated inputs. Thus, patches of cortex occupied exclusively by inputs representing one eye or the other could arise. In this scenario, ocular dominance column rearrangements in layer IV are generated by cooperation between inputs carrying *similar* patterns of activity, and competition between inputs carrying *dissimilar* patterns.

Monocular deprivation, which dramatically changes ocular dominance columns, clearly alters both the levels and patterns of neural activity between the two eyes. However, to specifically test the role of correlated activity in driving the competitive postnatal rearrangement of cortical connections, it is necessary to create a situation in which activity levels in each eye remain the same but the correlations between the two eyes are altered. This circumstance can be created in experimental animals by cutting one of the extraocular muscles in one eye. As already mentioned, this condition, in which the two eyes can no longer be aligned, is called strabismus. The major consequence of strabismus is that corresponding points on the two retinas are no longer stimulated by objects in the same location in visual space at the same time. As a result, differences in the visually evoked patterns of activity between the two eyes are far greater than normal. Unlike monocular deprivation, however, the overall amount of activity in each eye remains roughly the same; only the correlation of activity arising from corresponding retinal points is changed.

The effects of strabismus in experimental animals provide an illustration of the basic validity of Hebb's postulate. Recall that misalignment of the two eyes can, depending on the details of the situation, lead to suppression of the input from one and eventual loss of the related cortical connections. In other instances, however, input from the two eyes is retained. The anatomical pattern of ocular dominance columns in layer IV of cats in which input from both eyes remains (but is asynchronous) is sharper than normal, implying that the uncoordinated patterns of activity have actually accentuated the normal separation of cortical inputs from the two eyes. In addition, the ocular asynchrony prevents the binocular convergence that normally occurs in cells above and below layer IV: ocular dominance histograms from such animals show that most cells in *all* layers are driven exclusively by one eye *or* the other (Figure 23.9). Evidently, strabismus not only accentuates the competition between the two sets of thalamic inputs in layer IV, but also prevents binocular interactions in the other layers, which are mediated by local connections originating from cells in layer IV.

Even before visual experience exerts these effects, innate mechanisms have ensured that the basic outlines of a functional system are present. These intrinsic mechanisms establish the general circuitry required for vision, but allow modifications to accommodate the individual requirements that occur with changes in head size or eye alignment. Normal visual experience evidently validates the initial wiring, preserving, augmenting, or adjusting the normal arrangement. In the case of abnormal experience, such as monocular deprivation, the mechanisms that allow these adjustments result in more dramatic anatomical (and ultimately behavioral) changes, such as those that occur in amblyopia. The eventual decline of this capacity to remodel cortical (and subcortical) connections is presumably the cellular basis of critical periods in a variety of neural systems, including the development of language and other higher brain functions. By the same token, these differences in

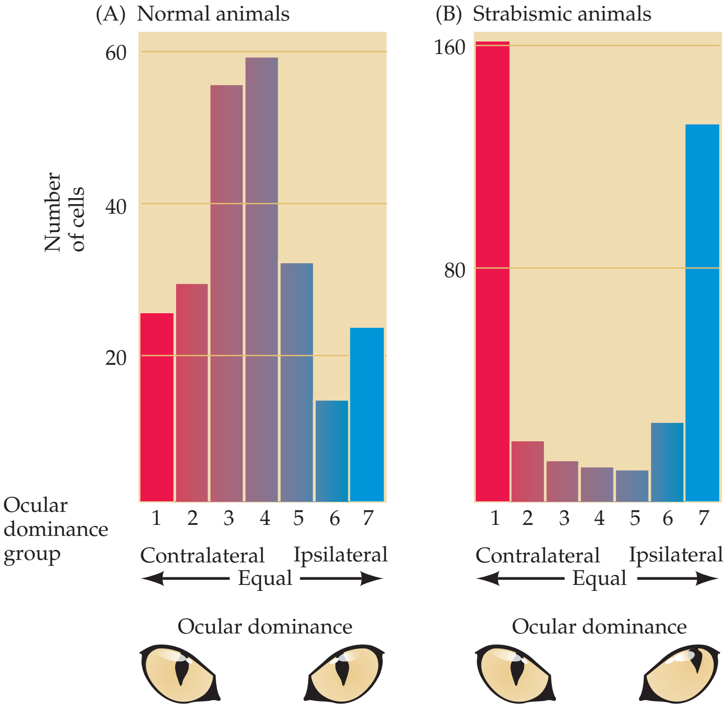


Figure 23.9 Ocular dominance histograms obtained by electrophysiological recordings in normal adult cats (A) and adults cats in which strabismus was induced during the critical period (B). The data in (A) is the same as that shown in Figure 23.3A. The number of binocular cells is sharply decreased as a consequence of strabismus; most of the cells are driven exclusively by stimulation of one eye or the other. This enhanced segregation of the inputs presumably results from the greater discrepancy in the patterns of activity between the two eyes as a result of surgically interfering with normal conjugate vision. (After Hubel and Wiesel, 1965.)

plasticity as a function of age presumably provide a neurobiological basis for the general observation that human behavior is much more susceptible to normal or pathological modification early in development than later on a concept with obvious educational, psychiatric, and social implications. Although many cellular and molecular mechanisms have been proposed to explain these effects (see Chapter 24), the specific mechanisms responsible for creating and eventually terminating critical periods remain largely unknown.

Cellular and Molecular Correlates of Activity-Dependent Plasticity during Critical Periods

A further question for understanding how experience changes neural circuits during critical periods is how patterns of activity are transduced to modify connections and to make these changes permanent. Clearly, the steps that initiate these processes must rely on signals generated by the synaptic activity associated with sensory experience or motor performance—the basic neural processes by which experience is represented. Neurotransmitters and a number of other signaling molecules, including neurotrophic factors, are obvious candidates for initiating changes that occur with correlated or repeated activity. Indeed, mice that lack genes for a number of neurotransmitters or receptors exhibit changes in experience-dependent visual cortical plasticity. These signals—neurotransmitters and other secreted molecules like neurotrophins—are all thought to ultimately influence levels of intracellular Ca^{2+}, particularly in postsynaptic cells (Figure 23.10). Increased Ca^{2+} concentration in the affected cells can activate a number of kinases, including Ca^{2+}/calmodulin kinase (CaMK) II, leading to phosphorylation-dependent modifications of the cytoskeleton and changes in dendritic and axonal branching. In addition, changes in Ca^{2+} can activate other kinases found in the nucleus, including CaMK IV (see Chapter 7). The kinases in the nucleus in turn can activate transcription factors like CREB (*c*yclic nucleotide *r*esponse *e*lement *b*inding transcription factor) via phosphorylation. When activation occurs, these DNA binding proteins can then influence gene expression, and thus alter the transcriptional state of the neuron to reflect experience-driven functional changes. Such changes may include—but are unlikely to be limited to—transcription of neurotrophin genes like *BDNF*. Whether this sequence is correct or complete remains uncertain, but it provides a plausible scenario for the molecular and cellular events underlying activity-dependent plasticity.

Evidence for Critical Periods in Other Sensory Systems

Although the neural basis of critical periods has been most thoroughly studied in the mammalian visual system, similar phenomena exist in a number of sensory systems, including the auditory, somatic sensory and olfactory systems. In the auditory system, experiments on the role of auditory experience and neural activity in owls (who use auditory information to localize prey) indicate that neural circuits for auditory localization are similarly shaped by experience. Thus, deafening an owl or altering neural activity during early postnatal development compromises the bird's ability to localize sounds and can alter the neural circuits that mediate this capacity. The development of song in many species of birds provides another auditory example, as described in Chapter 12. In the somatic sensory system, cortical maps can be changed by experience during a critical period of postnatal

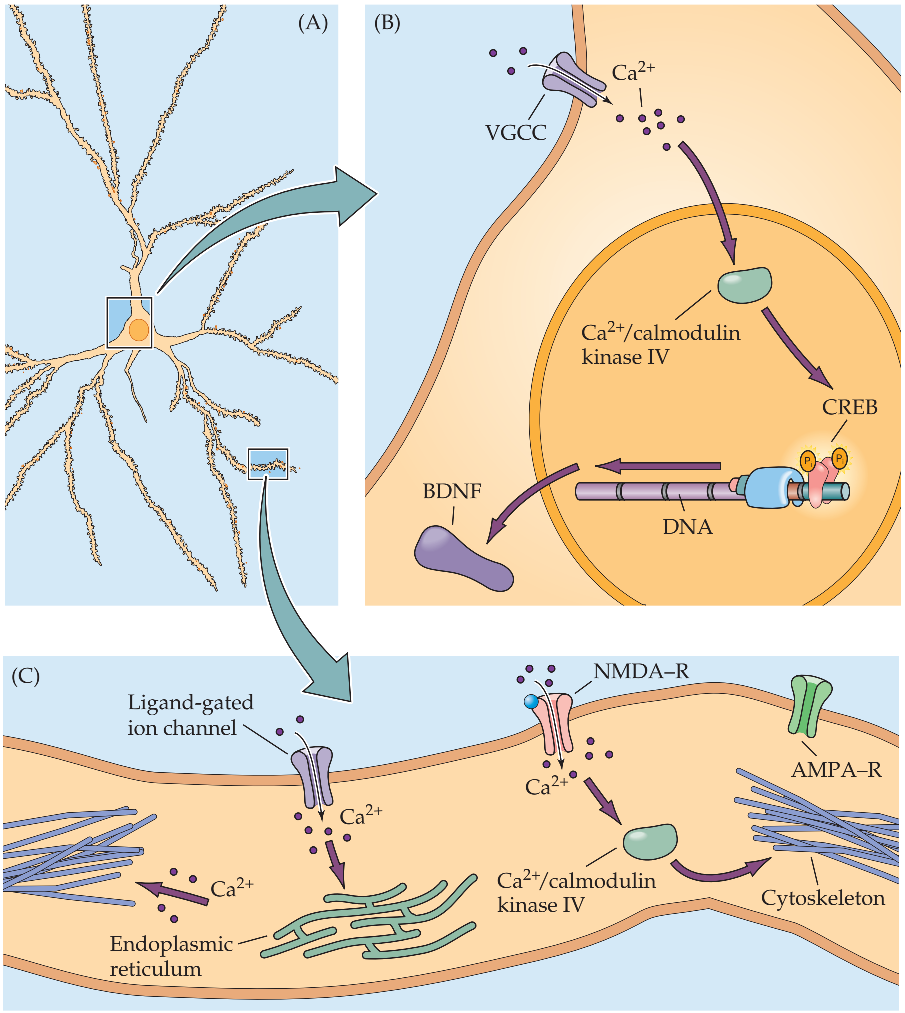


Figure 23.10 Transduction of electrical activity into cellular change via Ca^{2+} signaling. (A) A target neuron, showing two possible sites of action—the cell soma and the distal dendrites—for activity-dependent increases in Ca^{2+} signaling. (B) Correlated or sustained activity leads to increased Ca^{2+} conductances and increased intracellular Ca^{2+} concentration, which results in activation of Ca^{2+}/calmodulin kinase IV (CaMKIV) in the nucleus. CaMKIV then activates Ca^{2+}-regulated transcription factors like CREB. The target genes for activated CREB may include neurotrophic signals like BDNF, which when secreted by a cell may help stabilize or promote the growth of active synapses on that cell. (C) Local increases in Ca^{2+} signaling in distal dendrites due to correlated or sustained activity may lead to local increases in Ca^{2+} concentration which, via kinases like CaMKIV, modify cytoskeletal elements (actin- or tubulin-based structures). Changes in these elements lead to local changes in dendritic structure. In addition, increased local Ca^{2+} concentration may influence local translation of transcripts in the endoplasmic reticulum (ER), including transcripts for neurotransmitter receptors and other modulators of postsynaptic responses. Increased Ca^{2+} may also influence the trafficking of these proteins, their interaction with local scaffolds for cytoplasmic proteins, and their insertion into the postsynaptic membrane. (After Wong and Ghosh, 2002.)

development. In mice or rats, for instance, the anatomical patterns of “whisker barrels” in the somatic sensory cortex (see Chapter 8) can be altered by abnormal sensory experience during a narrow window in early postnatal life. And, as outlined in Chapter 14, behavioral studies in the olfactory system indicate that exposure to maternal odors for a limited period can alter the ability to respond to such odorants, a change that can persist throughout life. Clearly, the phenomenon of critical periods is general in development of sensory perceptual abilities and motor skills.

Summary

An individual animal’s history of interaction with the environment—its “experience”—helps to shape neural circuitry and thus determines subsequent behavior. In some cases, experience functions primarily as a switch to activate innate behaviors. More often, however, experience during a specific time in early life (referred to as a “critical period”) helps shape the adult behavioral repertoire. Critical periods influence behaviors as diverse as maternal bonding and the acquisition of language. Although it is possible to define the behavioral consequences of critical periods for these complex functions, their biological basis has been more difficult to understand. The most accessible and thoroughly studied example of a critical period is the one pertinent to the establishment of normal vision. These studies show that experience is translated into patterns of neuronal activity that influence the function and connectivity of the relevant neurons. In the visual system, and other systems as well, competition between inputs with different patterns of activity is an important determinant of adult connectivity. Correlated patterns of activity in afferent axons tend to stabilize connections and conversely a lack of correlated activity can weaken or eliminate connections. When normal patterns of activity are disturbed during a critical period in early life (experimentally in animals or by pathology in humans), the connectivity in the visual cortex is altered, as is visual function. If not reversed before the end of the critical period, these structural and functional alterations of brain circuitry are difficult or impossible to change. In normal development, the influence of activity on neural connectivity presumably enables the maturing brain to store the vast amounts of information that reflect the specific experience of the individual.

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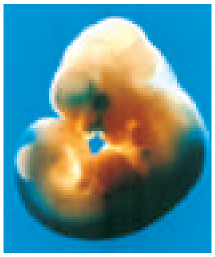
Chapter 24



Plasticity of Mature Synapses and Circuits

Overview

The capacity of the nervous system to change—generally referred to as neural plasticity—is obvious during the development of neural circuits. However, the adult brain must also possess substantial plasticity in order to learn new skills, establish new memories, and respond to injury throughout life. Although the mechanisms responsible for ongoing changes in the adult brain are not completely understood, altered neural function in maturity appears to rely primarily on carefully regulated changes in the strength of existing synapses. Experiments carried out in a variety of animals, ranging from sea slugs to primates, have shown that synaptic strength can be altered over periods that range from milliseconds to months. The molecular mechanisms underlying these changes are post-translational modifications of proteins and, in the case of longer-lasting effects, changes in gene expression. To some extent, changes in synaptic circuitry can also occur by localized formation of new axon terminals and dendritic processes. More extensive changes occur when the adult nervous system is damaged by trauma or disease, although regeneration of connections in the brain and spinal cord is sharply limited. Modest optimism regarding this unfortunate clinical situation is warranted by the observation that new neurons can be generated throughout life in a limited number of brain regions, suggesting that new cells can be integrated into existing circuits.

Synaptic Plasticity Underlies Behavioral Modification in Invertebrates

An obvious obstacle to exploring change in the brains of humans and other mammals is the enormous number of neurons and the complexity of synaptic connections. As a consequence, it is difficult to unambiguously attribute a behavioral modification to changes in the properties of specific neurons or synapses. One way to circumvent this dilemma is to examine plasticity in far simpler nervous systems. The assumption in this strategy is that plasticity is so fundamental that its essential cellular and molecular underpinnings are likely to be conserved in the nervous systems of very different organisms.

One of the most successful examples of this approach has been that of Eric Kandel and his colleagues at Columbia University using the marine mollusk *Aplysia californica* (Figure 24.1A). This sea slug has only a few tens of thousands of neurons, many of which are quite large (up to 1 mm in diameter) and in stereotyped locations within the ganglia that make up the animal's nervous system (Figure 24.1B). These attributes make it practical to monitor the electrical and chemical signaling of specific, identifiable nerve

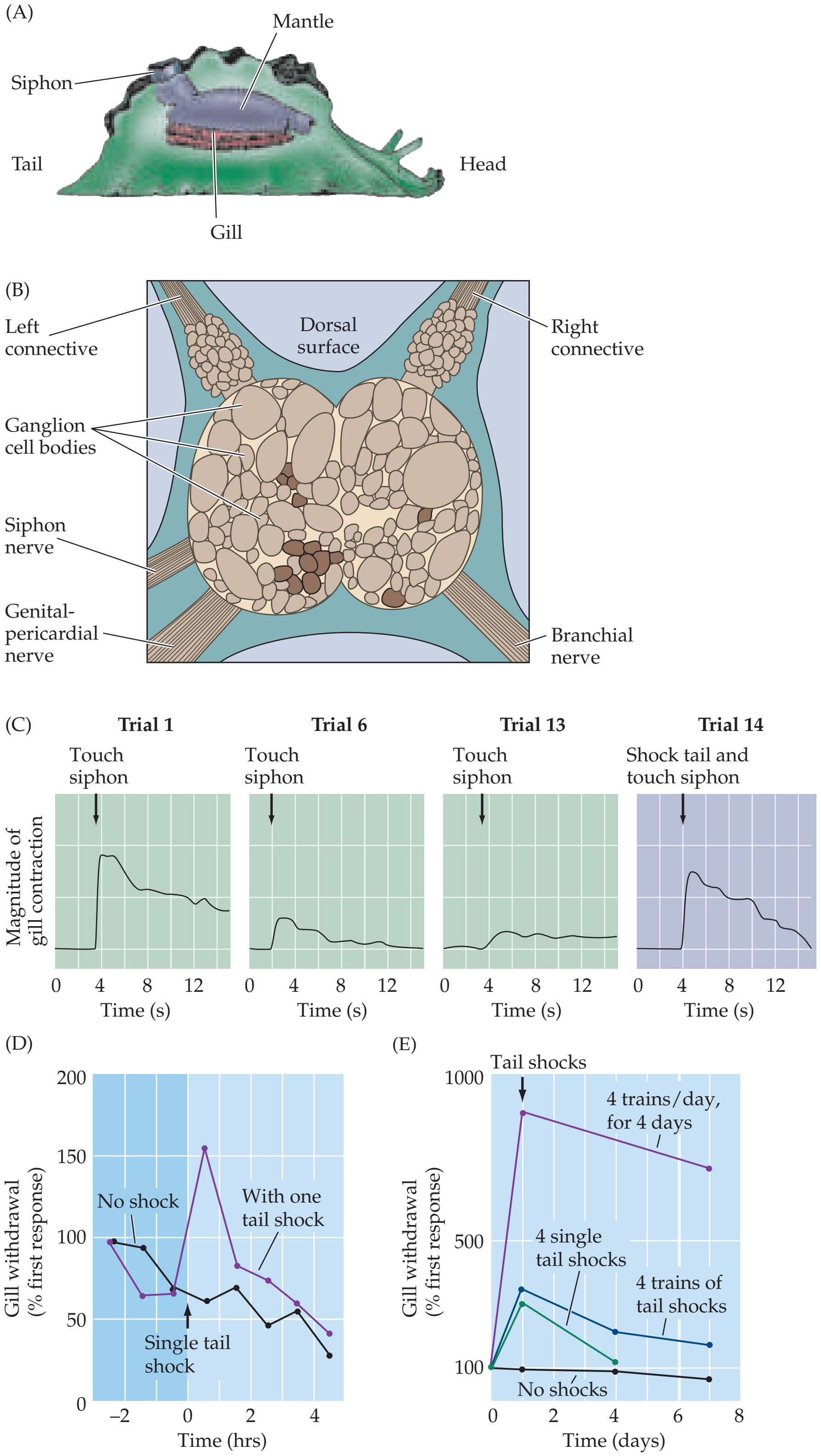


Figure 24.1 Short-term sensitization of the *Aplysia* gill withdrawal reflex. (A) Diagram of the animal. (B) The abdominal ganglion of *Aplysia.* The cell bodies of many of the neurons involved in gill withdrawal can be recognized by their size, shape, and position within this ganglion. (C) Changes in the gill withdrawal behavior due to habituation and sensitization. The first time that the siphon is touched, the gill contracts vigorously. Repeated touches elicit smaller gill contractions due to habituation. Subsequently pairing a siphon touch with an electrical shock to the tail restores a large and rapid gill contraction, due to short-term sensitization. (D) A short-term sensitization of the gill withdrawal response is observed following the pairing of a single tail shock with a siphon touch. (E) Repeated applications of tail shocks causes prolonged sensitization of the gill withdrawal response. (After Squire and Kandel, 1999.)

cells, and to define the synaptic circuits involved in mediating the limited behavioral repertoire of *Aplysia*.

Aplysia exhibit several elementary forms of behavioral plasticity. One form is **habituation**, a process that causes the animal to become less responsive to repeated occurrences of a stimulus. Habituation is found in many other species, including humans. For example, when dressing we initially experience tactile sensations due to clothes stimulating our skin, but habituation quickly causes these sensations to fade. Similarly, a light touch to the siphon of an *Aplysia* results in withdrawal of the animal's gill, but habituation causes the gill withdrawal to become weaker during repeated stimulation of the siphon (Figure 24.1C). The gill withdrawal response of *Aplysia* exhibits another form of plasticity called **sensitization.** Sensitization is a process that allows an animal to generalize an aversive response elicited by a noxious stimulus to a variety of other, non-noxious stimuli. In *Aplysia* that have habituated to siphon touching, sensitization of gill withdrawal is elicited by pairing a strong electrical stimulus to the animal's tail with another light touch of the siphon. This pairing causes the siphon stimulus to again elicit a strong withdrawal of the gill (Figure 24.1C, right) because the noxious stimulus to the tail sensitizes the gill withdrawal reflex to light touch. Even after a single stimulus to the tail, the gill withdrawal reflex remains enhanced for at least an hour (Figure 24.1D). With repeated pairing of tail and siphon stimuli, this behavior can be altered for days or weeks (Figure 24.1E), demonstrating a simple form of long-term memory.

The small number of neurons in the *Aplysia* nervous system makes it possible to define the neural circuits involved in gill withdrawal and to monitor the activity of individual neurons in these circuits. Although hundreds of neurons are ultimately involved in producing this simple behavior, the activities of only a few different types of neurons can account for gill withdrawal and its plasticity during habituation and sensitization. These critical neurons include mechanosensory neurons that innervate the siphon, motor neurons that innervate muscles in the gill, and interneurons that receive inputs from a variety of sensory neurons (Figure 24.2A). Touching the siphon activates the mechanosensory neurons, which form excitatory synapses that release glutamate onto both the interneurons and the motor neurons; thus, touching the siphon increases the probability that both these postsynaptic targets will produce action potentials. The interneurons form excitatory synapses on motor neurons, further increasing the likelihood of the motor neurons firing action potentials in response to mechanical stimulation of the siphon. When the motor neurons are activated by the summed synaptic excitation of the sensory neurons and interneurons, they release acetylcholine that excites the muscle cells of the gill, producing gill withdrawal.

Synaptic activity in this circuit is modified during habituation and sensitization. During habituation, transmission at the glutamatergic synapse between the sensory and motor neurons is decreased (Figure 24.2B, left). This weakening of synaptic transmission, termed **synaptic depression**, is thought to be responsible for the decreasing ability of siphon stimuli to evoke gill contractions during habituation. Synaptic depression has subsequently been shown to be due to a reduction in the number of synaptic vesicles available for release, with a concomitant reduction in the amount of glutamate released from the presynaptic sensory neuron. In contrast, sensitization modifies the function of this circuit by recruiting additional neurons. The tail shock that evokes sensitization activates sensory neurons that innervate the tail. These sensory neurons in turn excite modulatory

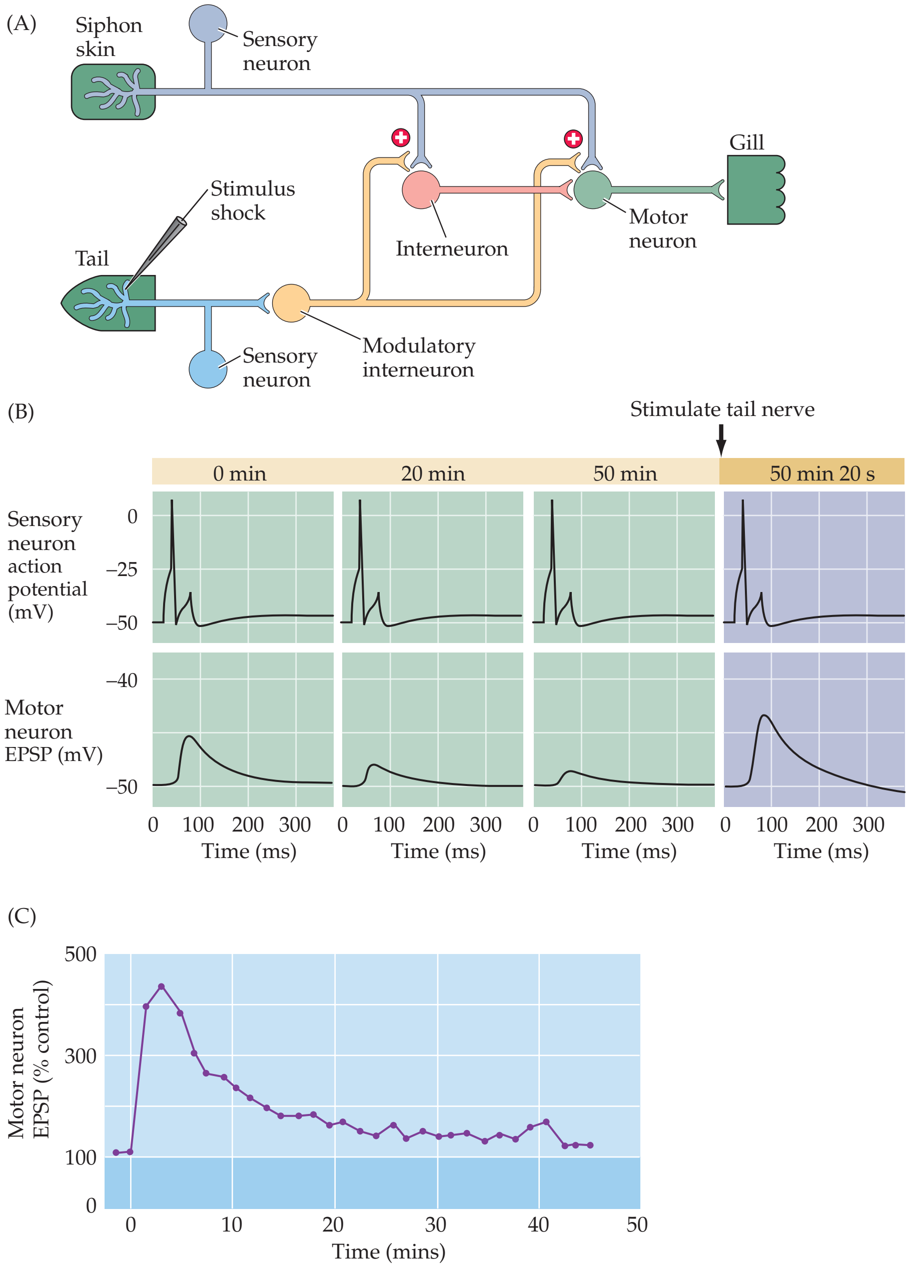

(A)
Siphon skin
Sensory neuron
Gill
Stimulus shock
Interneuron
Motor neuron
Tail
Sensory neuron
Modulatory interneuron
(B)
Stimulate tail nerve
0 min
20 min
50 min
50 min 20 s
Sensory neuron action potential (mV)
0
–25
–50
Motor neuron EPSP (mV)
–40
–50
0 100 200 300
Time (ms)
(C)
Motor neuron EPSP (% control)
500
300
100
0
0 10 20 30 40 50
Time (mins)

Figure 24.2 Synaptic mechanisms underlying short-term sensitization. (A) Neural circuitry involved in sensitization. Normally, touching the siphon skin activates sensory neurons that excite interneurons and gill motor neurons, yielding a contraction of the gill muscle. A shock to the animal's tail stimulates modulatory interneurons that alter synaptic transmission between the siphon sensory neurons and gill motor neurons, resulting in sensitization. (B) Changes in synaptic efficacy at the sensory-motor synapse during short-term sensitization. Prior to sensitization, activating the siphon sensory neurons causes an EPSP to occur in the gill motor neurons. Activation of the serotonergic modulatory interneurons enhances release of transmitter from the sensory neurons onto the motor neurons, increasing the EPSP in the motor neurons and causing the motor neurons to more strongly excite the gill muscle. (C) Time course of the serotonin-induced facilitation of transmission at the sensory motor synapse. (After Squire and Kandel, 1999.)

interneurons that release serotonin on to the presynaptic terminals of the sensory neurons of the siphon (see Figure 24.2A). Serotonin enhances transmitter release from the siphon sensory neuron terminals, leading to increased synaptic excitation of the motor neurons (Figure 24.2B). This modulation of the sensory neuron-motor neuron synapse lasts approximately an hour (Figure 24.2C), which is similar to the duration of the short-term sensitization of gill withdrawal produced by applying a single stimulus to the tail (Figure 24.1D). Thus, the short-term sensitization apparently is due to recruitment of additional synaptic elements that modulate synaptic transmission in the gill withdrawal circuit.

The mechanism thought to be responsible for the enhancement of glutamatergic transmission during short-term sensitization is shown in Figure 24.3A. Serotonin released by the facilitatory interneurons binds to G-protein-coupled receptors on the presynaptic terminals of the siphon sensory neurons (step 1), which stimulates production of the second messenger, cAMP (step 2). cAMP binds to the regulatory subunits of protein kinase A (PKA; step 3), liberating catalytic subunits of PKA that are then able to phosphorylate several proteins, probably including K^+ channels (step 4). The net effect of the action of PKA is to reduce the probability that the K^+ channels open during a presynaptic action potential. This effect prolongs the presynaptic action potential, thereby opening more presynaptic Ca^{2+} channels (step 5). Finally, the enhanced influx of Ca^{2+} into the presynaptic terminals increases the amount of transmitter released onto motor neurons during a sensory neuron action potential (step 6). In summary, short-term sensitization of gill withdrawal is mediated by a signal transduction cascade that involves neurotransmitters, second messengers, one or more protein kinases, and ion channels. This cascade ultimately enhances synaptic transmission between the sensory and motor neurons within the gill withdrawal circuit.

The same serotonin-induced enhancement of glutamate release that mediates short-term sensitization is also thought to underlie long-term sensitization. However, during long-term sensitization this circuitry is affected for up to several weeks. The prolonged duration of this form of plasticity is evidently due to changes in gene expression and thus protein synthesis (Figure 24.3B). With repeated training (that is, additional tail shocks), the serotonin-activated PKA involved in short-term sensitization now phosphorylates—and thereby activates—the transcriptional activator CREB (see Chapter 7). CREB binding to the cAMP responsive elements (CREs) in regulatory regions of nuclear DNA increases the rate of transcription of downstream genes. Although the changes in genes and gene products that follow CRE activation have been difficult to sort out, two consequences of gene activation have been identified. First, CREB stimulates the synthesis of an enzyme, ubiquitin hydroxylase, that stimulates degradation of the regulatory subunit of PKA. This causes a persistent increase in the amount of free catalytic subunit, meaning that some PKA is persistently active and no longer requires serotonin to be activated. CREB also stimulates another transcriptional activator protein, called C/EBP. C/EBP stimulates transcription of other, unknown genes that cause addition of synaptic terminals, yielding a long-term increase in the number of synapses between the sensory and the motor neurons. Such structural increases are not seen following short-term sensitization and may represent the ultimate cause of the long-lasting change in overall strength of the relevant circuit connections that produce a long-lasting enhancement in the gill withdrawal response.

These studies of *Aplysia*, and related work on other invertebrates such as the fruit fly (Box A), have led to several generalizations about the neural mechanisms underlying plasticity in the adult nervous system that presumably extend to mammals and other vertebrates. First, behavioral plasticity can clearly arise from plastic changes in the efficacy of synaptic transmission. Second, these changes in synaptic function can be either short-term effects that rely on post-translational modification of existing synaptic proteins, or long-term changes that require changes in gene expression, new protein synthesis, and perhaps even growth of new synapses (or the elimination of existing ones). The following sections explore the evidence for these generalizations in neuronal circuits and synapses of the mature mammalian nervous system.

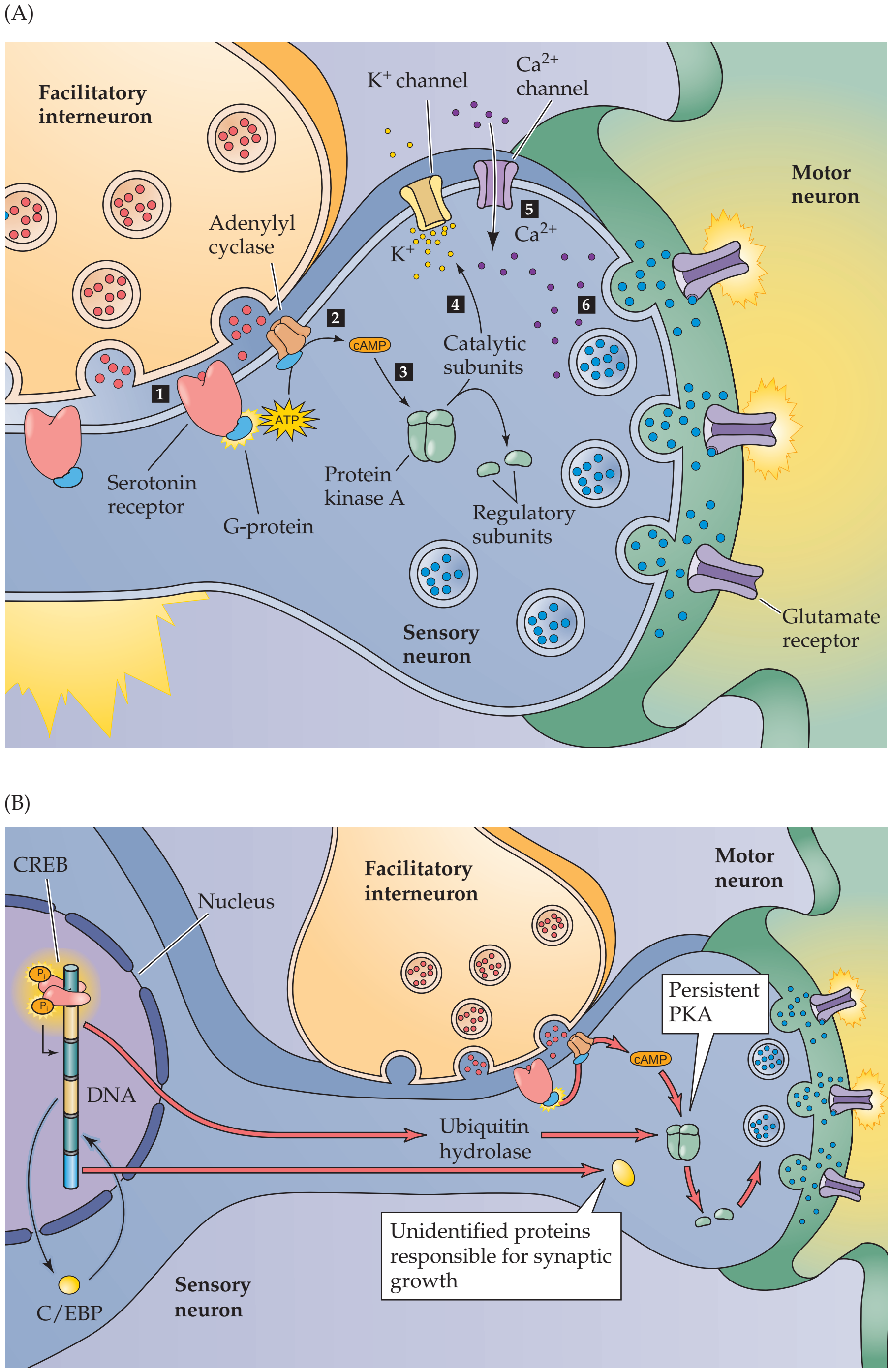

(A)
Facilitatory interneuron
K+ channel
Ca2+ channel
Motor neuron
Adenylyl cyclase
5
Ca2+
K+
4
6
2
cAMP
Catalytic subunits
3
1
ATP
Serotonin receptor
G-protein
Protein kinase A
Regulatory subunits
Sensory neuron
Glutamate receptor
(B)
CREB
Nucleus
Facilitatory interneuron
Motor neuron
P
P
DNA
Persistent PKA
cAMP
Ubiquitin hydrolase
Unidentified proteins responsible for synaptic growth
C/EBP
Sensory neuron

Figure 24.3 Mechanism of presynaptic enhancement underlying behavioral sensitization. (A) Short-term sensitization is due to an acute, PKA-dependent enhancement of glutamate release from the presynaptic terminals of sensory neurons. See text for explanation. (B) Long-term sensitization is due to changes in gene expression, causing expression of proteins that change PKA activity and lead to changes in synapse growth. (After Squire and Kandel, 1999.)

Box A

Genetics of Learning and Memory in the Fruit Fly

As part of a renaissance in the genetic analysis of simple organisms in the mid-1970s, several investigators recognized that the genetic basis of learning and memory might be effectively studied in the fruit fly, *Drosophila melanogaster*. In the intervening quarter-century, this approach has yielded some fundamental insights. Although learning and memory has certainly been one of the more difficult problems tackled by *Drosophila* geneticists, their efforts have been surprisingly successful. A number of genetic mutations have been discovered that to alter learning and memory, and the identification of these genes has provided a valuable framework for studying the cellular mechanisms of these processes.

The initial problem in this work was to develop behavioral tests that could identify abnormal learning and/or memory defects in large populations of flies. This challenge was met by Seymour Benzer and his colleagues Chip Quinn and Bill Harris at the California Institute of Technology, who developed the olfactory and visual learning tests that have become the basis for most subsequent analyses of learning and memory in the fruit fly (see figure). Behavioral paradigms pairing odors or light with an aversive stimulus allowed Benzer and his colleagues to assess associative learning in flies. The design of an ingenious testing apparatus controlled for non-learning-related sensory cues that had previously complicated such behavioral testing. Moreover, the apparatus allowed large numbers of flies to be screened relatively easily, expediting the analysis of mutagenized populations.

These studies led to the identification of an ever-increasing number of single gene mutations that disrupt learning and/or memory in flies. The behavioral and molecular studies of the mutants (given whimsical but descriptive names like dunce, rutabaga, and amnesiac) suggested that a central pathway for learning and memory in the fly is signal transduction mediated by the cyclic nucleotide cAMP. Thus, the gene products of the *dunce*, *rutabaga*, and *amnesiac* loci are, respectively, a phosphodiesterase (which degrades cAMP), an adenylyl cyclase (which converts ATP to cAMP), and a peptide transmitter that stimulates adenylyl cyclase. This conclusion about the importance of cAMP has been confirmed by the finding that genetic manipulation of the CREB transcription factor also interferes with learning and memory in normal flies.

These observations in *Drosophila* accord with conclusions reached in studies of *Aplysia* and mammals (see text) and have emphasized the importance of cAMP-mediated learning and memory in a wide range of additional species.

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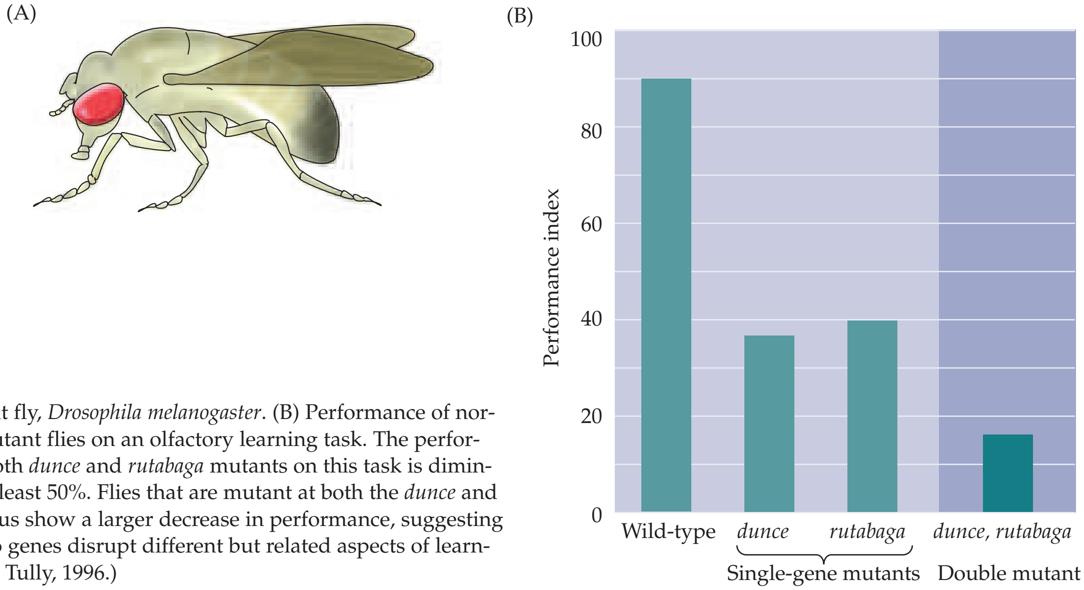


(A) The fruit fly, *Drosophila melanogaster*. (B) Performance of normal and mutant flies on an olfactory learning task. The performance of both *dunce* and *rutabaga* mutants on this task is diminished by at least 50%. Flies that are mutant at both the *dunce* and *rutabaga* locus show a larger decrease in performance, suggesting that the two genes disrupt different but related aspects of learning. (B after Tully, 1996.)

Short-Term Synaptic Plasticity in the Mammalian Nervous System

Evidence for synaptic plasticity in the mammalian nervous system is widespread; indeed, it is probably safe to conclude that *all* chemical synapses are capable of plastic change. Synaptic plasticity mechanisms at mammalian synapses, like their invertebrate counterparts, occur on time scales ranging from milliseconds to days, weeks, or longer. The short-term forms of plasticity—those lasting for minutes or less—have been studied in greatest detail at peripheral neuromuscular synapses, the same synapses that proved so valuable for understanding basic mechanisms of synaptic transmission (Chapter 5).

Repeated activation of the neuromuscular junction triggers several changes that vary in both direction and duration (Figure 24.4). **Synaptic facilitation**, which is a transient increase in synaptic strength, occurs when two or more action potentials invade the presynaptic terminal in close succession. Facilitation results in more neurotransmitter being released by each succeeding action potential, causing the postsynaptic end plate potential (EPP) to increase progressively. Synaptic facilitation is most likely the result of prolonged elevation of presynaptic calcium levels following synaptic activity. Although the entry of Ca^{2+} into the presynaptic terminal occurs within a millisecond or two after an action potential invades (see Chapter 5), the mechanisms that return Ca^{2+} to resting levels are much slower. Thus, when action potentials arrive close together in time, calcium builds up within the terminal and allows more neurotransmitter to be released by a subsequent presynaptic action potential. A high-frequency burst of presynaptic action potentials (referred to as tetanus) can yield an even more prolonged elevation of presynaptic calcium levels, causing another form of synaptic plasticity called **post-tetanic potentiation** (**PTP**). PTP is delayed in its onset and typically enhances transmitter release for up to a few minutes after the train of stimuli ends. The difference in duration distinguishes PTP from synaptic facilitation. PTP also is thought to arise from calcium-dependent processes, perhaps including activation of presynaptic protein kinases, that enhance the ability of incoming calcium ions to trigger fusion of synaptic vesicles with the plasma membrane.

Synaptic transmission also can be diminished following repeated synaptic activity. Such **synaptic depression** occurs when many presynaptic action potentials occur in rapid succession and depends on the amount of neurotransmitter that has been released (see Figure 24.4). Depression arises because of the progressive depletion of the pool of synaptic vesicles available for fusion in this circumstance. During synaptic depression, the strength of the synapse declines until this pool can be replenished via the mechanisms involved in recycling of synaptic vesicles (see Chapter 5).

During repeated synaptic activity, these various types of plasticity can interact in complex ways. For example, at the neuromuscular synapse, repeated activity first facilitates synaptic transmission, and depletion of synaptic vesicles then allows depression to dominate and weaken the synapse (see Figure 24.4). After the stimulus train ends, the invasion of the terminal by another action potential causes enhanced transmitter release (i.e., post-tetanic potentiation). These forms of short-term plasticity are observed at virtually all chemical synapses and continually modify synaptic strength. Thus, the efficacy of chemical synaptic transmission changes dynamically as a consequence of the recent history of synaptic activity.

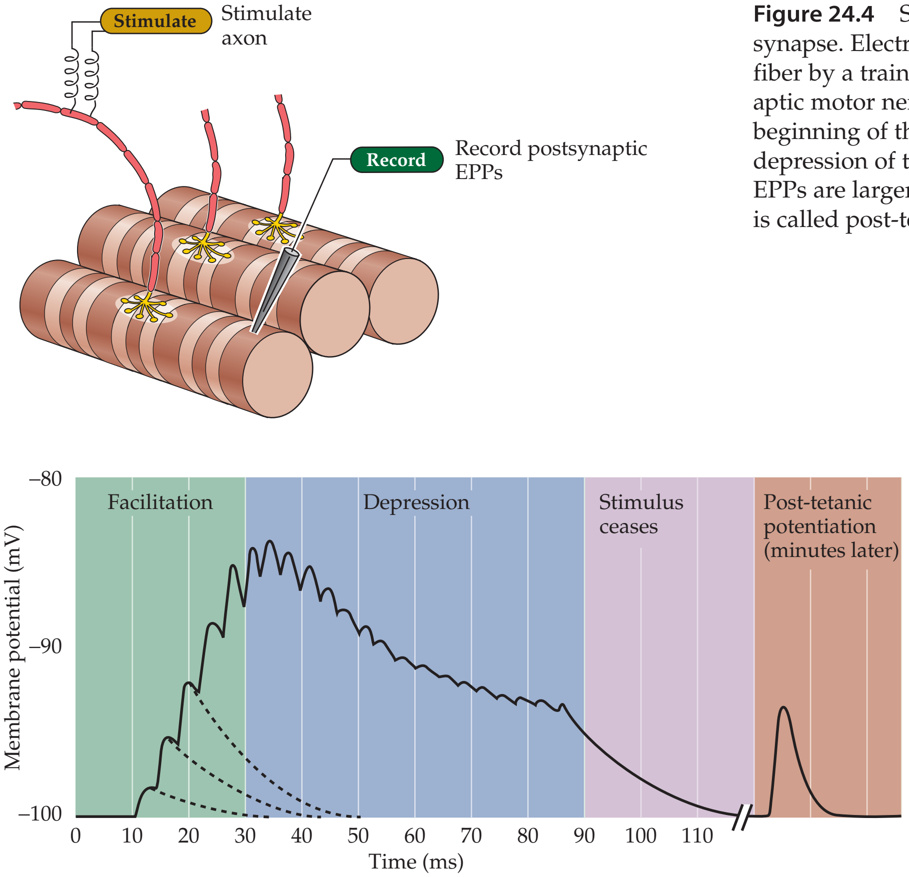


Figure 24.4 Short-term plasticity at the neuromuscular synapse. Electrical recording of EPPs elicited in a muscle fiber by a train of electrical stimuli applied to the presynaptic motor nerve. Facilitation of the EPP occurs at the beginning of the stimulus train and is followed by depression of the EPP. After the train of stimuli ends, EPPs are larger than before the train. This phenomenon is called post-tetanic potentiation. (After Katz, 1966.)

Long-Term Synaptic Plasticity in the Mammalian Nervous System

Facilitation, depression, and post-tetanic potentiation can briefly modify synaptic transmission. While these mechanisms are probably responsible for many short-lived changes in brain circuitry, they cannot provide the basis for memories or other manifestations of behavioral plasticity that persist for weeks, months, or years. As might be expected, many synapses in the mammalian central nervous system exhibit long-lasting forms of synaptic plasticity that are plausible substrates for more permanent changes in behavior. Because of their duration, these forms of synaptic plasticity are widely believed to be cellular correlates of learning and memory. Thus, a great deal of effort has gone into understanding how they are generated.

Some patterns of synaptic activity in the CNS produce a long-lasting increase in synaptic strength known as **long-term potentiation (LTP)**, whereas other patterns of activity produce a long-lasting decrease in synaptic strength, known as **long-term depression (LTD)**. LTP and LTD are broad terms that describe only the direction of change in synaptic efficacy; in fact, different cellular and molecular mechanisms can be involved in producing LTP or LTD at different synapses. In general, these different forms of synaptic plasticity are produced by different histories of activity, and are mediated by different complements of intracellular signal transduction pathways in the nerve cells involved.

Long-Term Potentiation of Hippocampal Synapses

LTP has been most thoroughly studied at excitatory synapses in the mammalian hippocampus, an area of the brain that is especially important in the formation and/or retrieval of some forms of memory (see Chapter 30). In humans, functional imaging shows that the human hippocampus is activated during certain kinds of memory tasks, and that damage to the hippocampus results in an inability to form certain types of new memories. In rodents, hippocampal neurons fire action potentials only when an animal is in certain locations. Such "place cells" appear to encode spatial memories, an interpretation supported by the fact that hippocampal damage prevents rats from developing proficiency in spatial learning tasks (see Figure 30.7). Although many other brain areas are involved in the complex process of memory formation, storage, and retrieval, these observations have led many investigators to study LTP of hippocampal synapses.

Work on LTP began in the late 1960s, when Terje Lomo and Timothy Bliss, working in the laboratory of Per Andersen in Oslo, Norway, discovered that a few seconds of high-frequency electrical stimulation can enhance synaptic transmission in the rabbit hippocampus for days or even weeks. More recently, however, progress in understanding the mechanism of LTP has relied heavily on in vitro studies of slices of living hippocampus. The arrangement of neurons allows the hippocampus to be sectioned such that most of the relevant circuitry is left intact. In such preparations, the cell bodies of the pyramidal neurons lie in a single densely packed layer that is readily apparent (Figure 24.5). This layer is divided into several distinct regions, the major ones being CA1 and CA3. "CA" refers to *cornu Ammon*, the Latin for Ammon's horn—the ram's horn that resembles the shape of the hip-

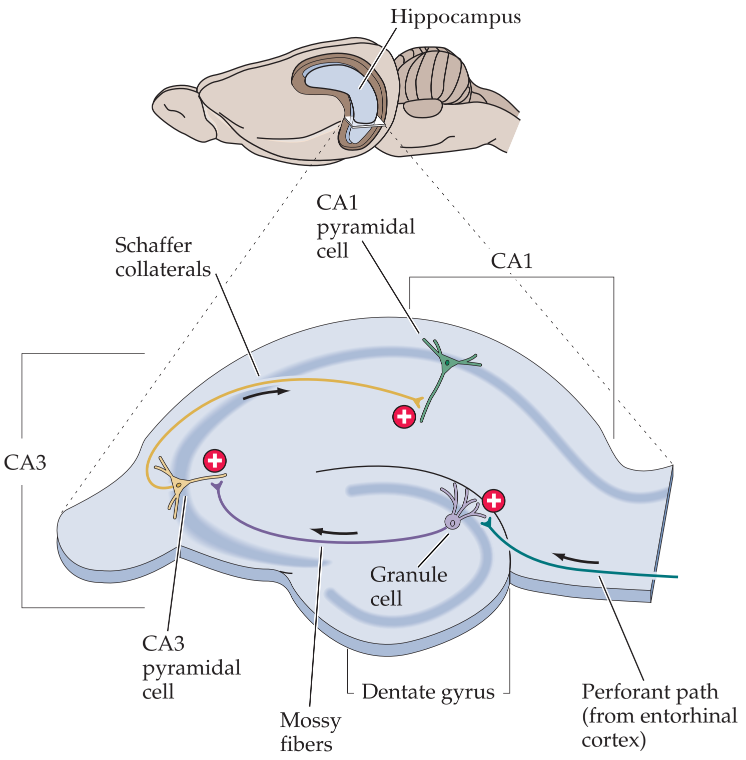


Figure 24.5 Diagram of a section through the rodent hippocampus showing the major regions, excitatory pathways, and synaptic connections. Long-term potentiation has been observed at each of the three synaptic connections shown here.

pocampus. The dendrites of pyramidal cells in the CA1 region form a thick band (the stratum radiatum), where they receive synapses from Schaffer collaterals, the axons of pyramidal cells in the CA3 region. Much of the work on LTP has focused on the synaptic connections between the Schaffer collaterals and CA1 pyramidal cells. Electrical stimulation of Schaffer collaterals generates excitatory postsynaptic potentials (EPSPs) in the postsynaptic CA1 cells (Figure 24.6A,B). If the Schaffer collaterals are stimulated only two or three times per minute, the size of the evoked EPSP in the CA1 neurons remains constant. However, a brief, high-frequency train of stimuli to the same axons causes LTP, which is evident as a long-lasting increase in EPSP amplitude (Figure 24.6C). LTP occurs not only at the excitatory synapses of the hippocampus shown in Figure 24.5, but at many other synapses in a variety of brain regions, including the cortex, amygdala, and cerebellum.

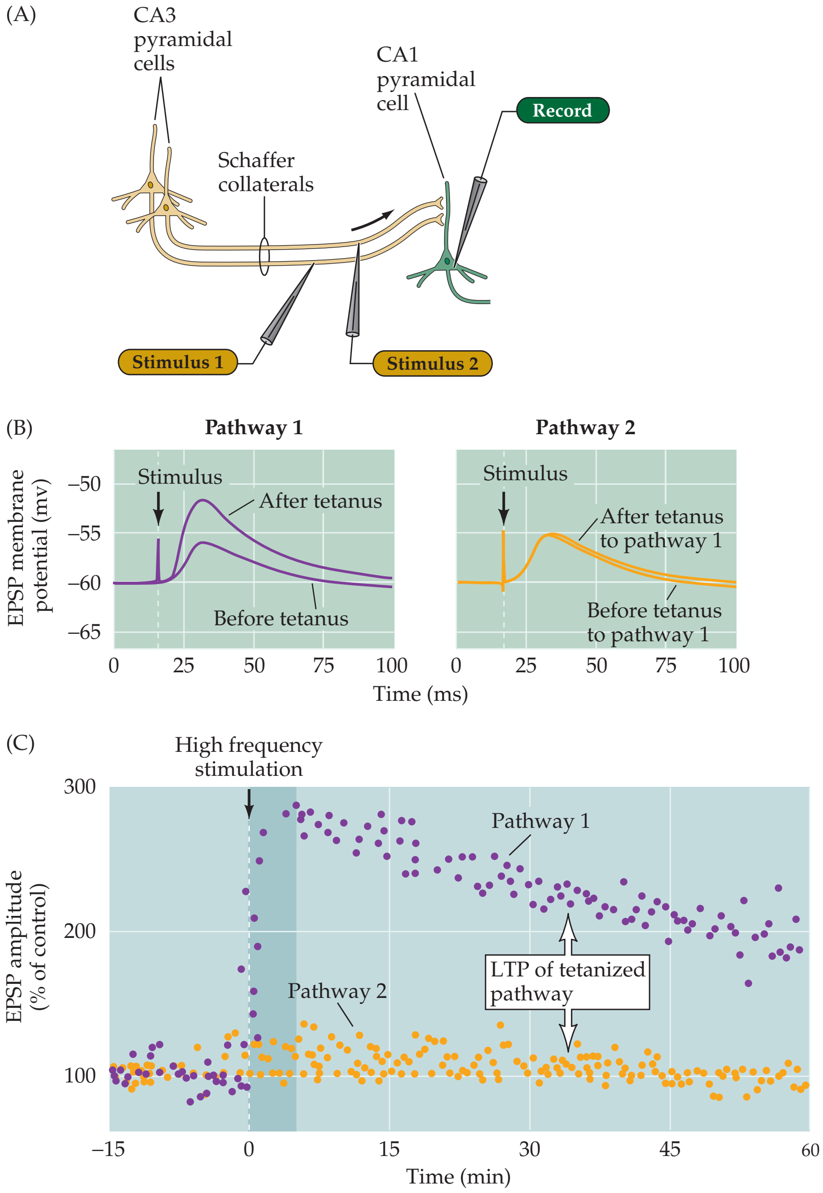


Figure 24.6 Long-term potentiation of Schaffer collateral-CA1 synapses. (A) Arrangement for recording synaptic transmission; two stimulating electrodes (1 and 2) each activate separate populations of Schaffer collaterals, thus providing test and control synaptic pathways. (B) Left: Synaptic responses recorded in a CA1 neuron in response to single stimuli of synaptic pathway 1, minutes before and one hour after a high-frequency train of stimuli. The high-frequency stimulus train increases the size of the EPSP evoked by a single stimulus. Right: Responses produced by stimulating synaptic pathway 2, which did not receive high-frequency stimulation, is unchanged. (C) The time course of changes in the amplitude of EPSPs evoked by stimulation of pathways 1 and 2. High-frequency stimulation of pathway 1 causes a prolonged enhancement of the EPSPs in this pathway (purple). This potentiation of synaptic transmission in pathway 1 persists for several hours, while the amplitude of EPSPs produced by pathway 2 (orange) remains constant. (After Malinow et al., 1989.)

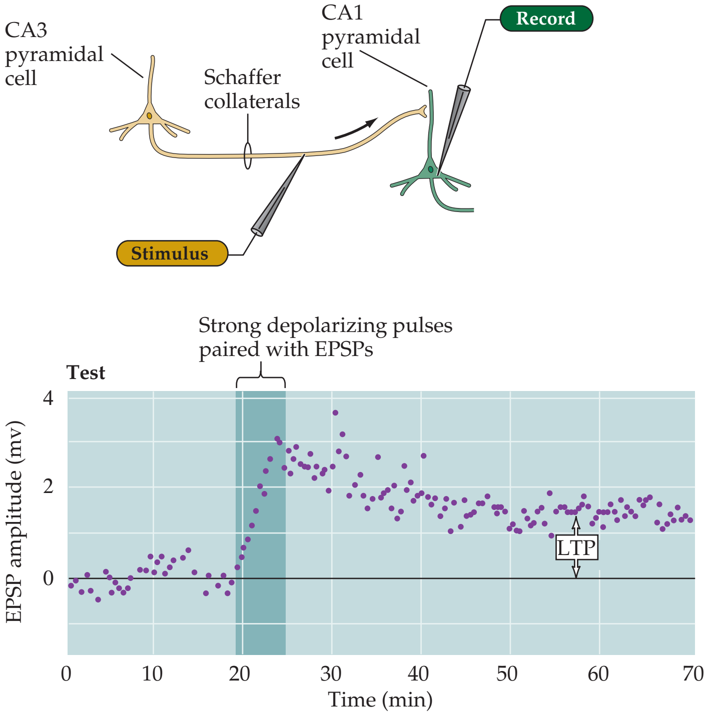


Figure 24.7 Pairing presynaptic and postsynaptic activity causes LTP. Single stimuli applied to a Schaffer collateral synaptic input evokes EPSPs in the postsynaptic CA1 neuron. These stimuli alone do not elicit any change in synaptic strength. However, when the CA1 neuron's membrane potential is briefly depolarized (by applying current pulses through the recording electrode) in conjunction with the Schaffer collateral stimuli, there is a persistent increase in the EPSPs. (After Gustafsson et al., 1987.)

LTP of the Schaffer collateral synapse exhibits several properties that make it an attractive neural mechanism for information storage. First, LTP is *state-dependent*: The state of the membrane potential of the postsynaptic cell determines whether or not LTP occurs (Figure 24.7). If a single stimulus to the Schaffer collaterals—which would not normally elicit LTP—is paired with strong depolarization of the postsynaptic CA1 cell, the activated Schaffer collateral synapses undergo LTP. The increase occurs only if the paired activities of the presynaptic and postsynaptic cells are tightly linked in time, such that the strong postsynaptic depolarization occurs within about 100 ms of presynaptic transmitter release. Recall that a requirement for coincident activation of presynaptic and postsynaptic elements is the central postulate of Donald Hebb's early theories of the synaptic changes underlying the selective maintenance of neuronal connections (see Chapter 22).

LTP also exhibits the property of *input specificity*: When LTP is induced by the stimulation of one synapse, it does not occur in other, inactive synapses that contact the same neuron (see Figure 24.6). Thus, LTP is restricted to activated synapses rather than to all of the synapses on a given cell (Figure 24.8A). This feature of LTP is consistent with its involvement in memory formation (or at least the storage of specific information). If activation of one set of synapses led to all other synapses—even inactive ones—being potentiated, it would be difficult to selectively enhance particular sets of inputs, as is presumably required to store specific information.

Another important property of LTP is **associativity** (Figure 24.8B). As noted, weak stimulation of a pathway will not by itself trigger LTP. However, if one pathway is weakly activated at the same time that a neighboring pathway onto the same cell is strongly activated, both synaptic pathways undergo LTP. This selective enhancement of conjointly activated sets of synaptic inputs is often considered a cellular analog of associative or classical

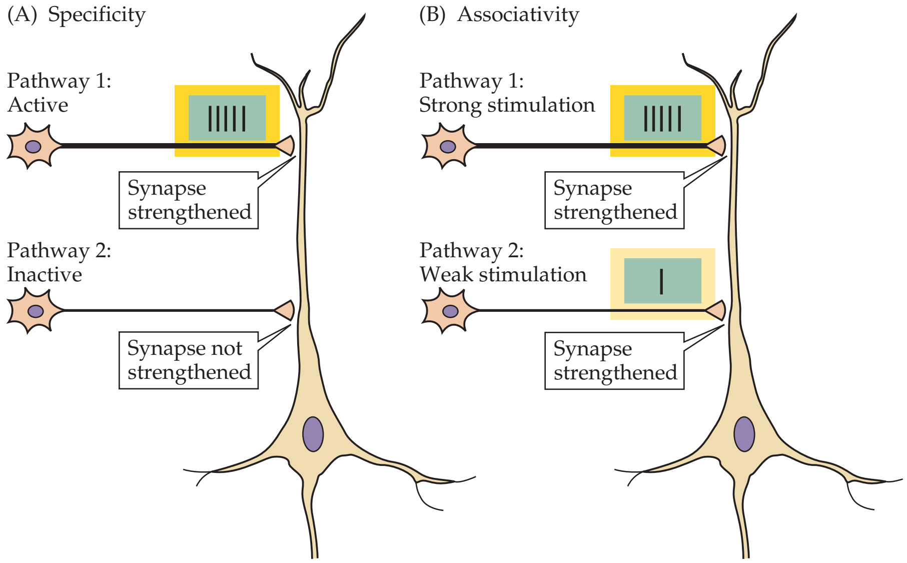


Figure 24.8 Properties of LTP at a CA1 pyramidal neuron receiving synaptic inputs from two independent sets of Schaffer collateral axons. (A) Strong activity initiates LTP at active synapses (pathway 1) without initiating LTP at nearby inactive synapses (pathway 2). (B) Weak stimulation of pathway 2 alone does not trigger LTP. However, when the same weak stimulus to pathway 2 is activated together with strong stimulation of pathway 1, both sets of synapses are strengthened.

conditioning. More generally, associativity is expected in any network of neurons that links one set of information with another.

Although there is clearly a gap between understanding LTP of hippocampal synapses and understanding learning, memory, or other aspects of behavioral plasticity in mammals, this form of synaptic plasticity provides a plausible neural mechanism for long-lasting changes in a part of the brain that is known to be involved in the formation of certain kinds of memories.

Molecular Mechanisms Underlying LTP

Despite the fact that LTP was discovered more than 30 years ago, its molecular underpinnings were not well understood until recently. A key advance in this effort occurred in the mid-1980s, when it was discovered that antagonists of the NMDA type of glutamate receptor prevent LTP, but have no effect on the synaptic response evoked by low-frequency stimulation of the Schaffer collaterals. At about the same time, the unique biophysical properties of the NMDA receptor were first appreciated. As described in Chapter 6, the NMDA receptor channel is permeable to Ca^{2+}, but is blocked by physiological concentrations of Mg^{2+}. This property provides a critical insight into how LTP is induced. Thus, during low-frequency synaptic transmission, glutamate released by the Schaffer collaterals binds to both NMDA-type and AMPA/kainate-type glutamate receptors. While both types of receptors bind glutamate, if the postsynaptic neuron is at its normal resting membrane potential, the NMDA channels will be blocked by Mg^{2+} ions and no current will flow (Figure 24.9, left). Because blockade of the NMDA channel by Mg^{2+} is voltage-dependent, the function of the synapse changes markedly when the postsynaptic cell is depolarized. Thus, conditions that induce LTP, such as high-frequency stimulation (as in Figure 24.6), will cause a prolonged depolarization that results in Mg^{2+} being expelled from the NMDA channel (Figure 24.9, right). Removal of Mg^{2+} allows Ca^{2+} to enter the postsynaptic neuron and the resulting increase in Ca^{2+} concentration within the dendritic spines of the postsynaptic cell turns out to be the trigger for LTP (Box B). The

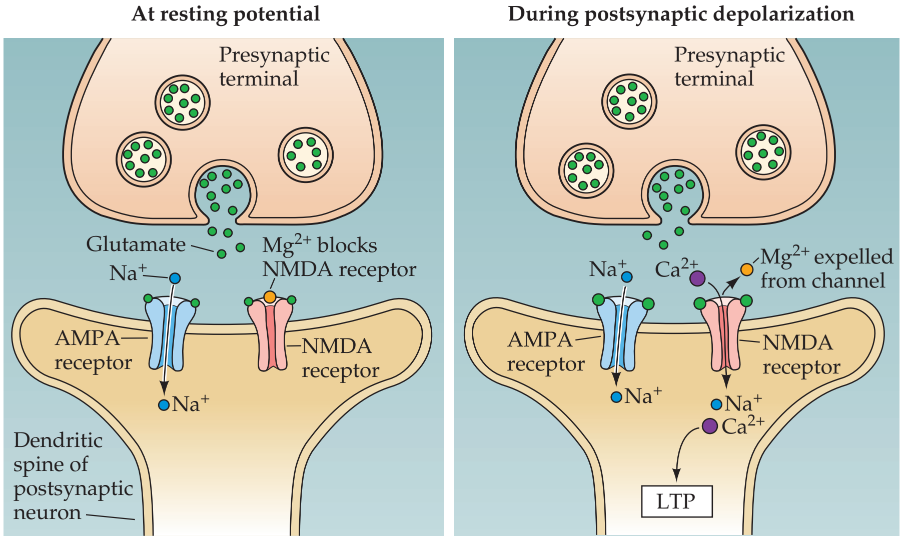

At resting potential
During postsynaptic depolarization
Presynaptic terminal
Presynaptic terminal
Glutamate
Na+
Mg2+ blocks NMDA receptor
AMPA receptor
NMDA receptor
Na+
Dendritic spine of postsynaptic neuron
Na+
Ca2+
Mg2+ expelled from channel
AMPA receptor
NMDA receptor
Na+
Na+
Ca2+
LTP

Figure 24.9 The NMDA receptor channel can open only during depolarization of the postsynaptic neuron from its normal resting level. Depolarization expels Mg^{2+} from the NMDA channel, allowing current to flow into the postsynaptic cell. This leads to Ca^{2+} entry, which in turn triggers LTP. (After Nicoll et al., 1988.)

NMDA receptor thus behaves like a molecular "*and*" gate: The channel opens (to induce LTP) only when glutamate is bound to NMDA receptors *and* the postsynaptic cell is depolarized to relieve the Mg^{2+} block of the NMDA channel. Thus, the NMDA receptor can detect the coincidence of two events.

These properties of the NMDA receptor can account for many of the characteristics of LTP. The specificity of LTP (see Figure 24.8A) can be explained by the fact that NMDA channels will be opened only at synaptic inputs that are active and releasing glutamate, thereby confining LTP to these sites. With respect to associativity (see Figure 24.8B), a weakly stimulated input releases glutamate, but cannot sufficiently depolarize the postsynaptic cell to relieve the Mg^{2+} block. If neighboring inputs are strongly stimulated, however, they provide the "associative" depolarization necessary to relieve the block. The state dependence of LTP, evident as the induction of LTP by the pairing of weak synaptic input with depolarization (see Figure 24.7), should work similarly: The synaptic input releases glutamate, while the coincident depolarization relieves the Mg^{2+} block of the NMDA receptor.

Several sorts of observations have confirmed that a rise in the concentration of Ca^{2+} in the postsynaptic CA1 neuron, due to Ca^{2+} ions entering through NMDA receptors, serves as a second messenger signal that induces LTP. Imaging studies, for instance, have shown that activation of NMDA receptors causes increases in postsynaptic Ca^{2+} levels. Furthermore, injection of Ca^{2+} chelators blocks LTP induction, whereas elevation of Ca^{2+} levels in postsynaptic neurons potentiates synaptic transmission. Ca^{2+} induces LTP by activating complicated signal transduction cascades that include protein kinases in the postsynaptic neuron. At least two Ca^{2+}-activated protein kinases have been implicated in LTP induction (Figure 24.10): Ca^{2+}/calmodulin-dependent protein kinase (CaMKII) and protein kinase C (PKC; see

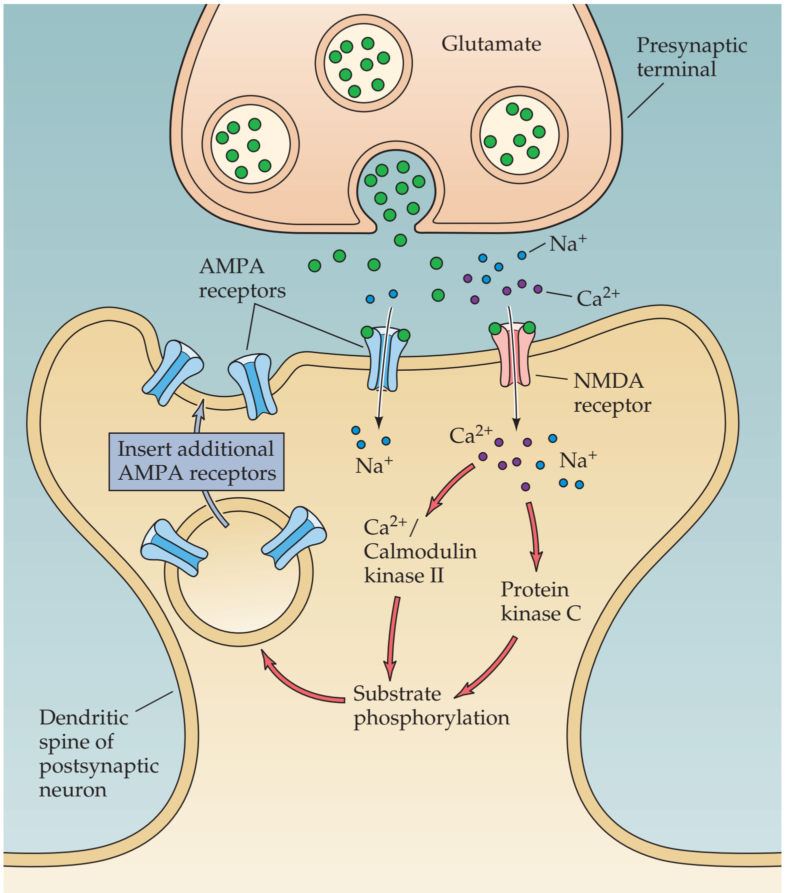

Glutamate
Presynaptic terminal
AMPA receptors
Na+
Ca2+
NMDA receptor
Insert additional AMPA receptors
Na+
Ca2+
Na+
Ca2+/ Calmodulin kinase II
Protein kinase C
Substrate phosphorylation
Dendritic spine of postsynaptic neuron

Figure 24.10 Mechanisms underlying LTP. During glutamate release, the NMDA channel opens only if the postsynaptic cell is sufficiently depolarized. The Ca^{2+} ions that enter the cell through the channel activate postsynaptic protein kinases. These kinases may act postsynaptically to insert new AMPA receptors into the postsynaptic spine, thereby increasing the sensitivity to glutamate.

Chapter 7). CaMKII seems to play an especially important role: This enzyme is the most abundant postsynaptic protein at Schaffer collateral synapses, and pharmacological inhibition or genetic deletion of CaMKII prevents LTP. The downstream targets of these kinases are not yet fully known, but apparently include the AMPA class of glutamate receptors.

Recent efforts have clarified the mechanism(s) responsible for the expression of LTP, namely how LTP causes synapses to be strengthened for prolonged periods. The most likely explanation is that LTP arises from changes in the sensitivity of the postsynaptic cell to glutamate. Several recent observations indicate that excitatory synapses can dynamically regulate their postsynaptic glutamate receptors and can even add new AMPA receptors to “silent” synapses that did not previously have postsynaptic AMPA receptors (Box C). The “expression” or maintenance of LTP apparently is due to such insertion of AMPA receptors into the postsynaptic membrane (as opposed to its “induction,” which relies on the activity of the NMDA receptors). For example, synaptic activity that induces LTP can elicit postsynaptic responses

Box B

Dendritic Spines

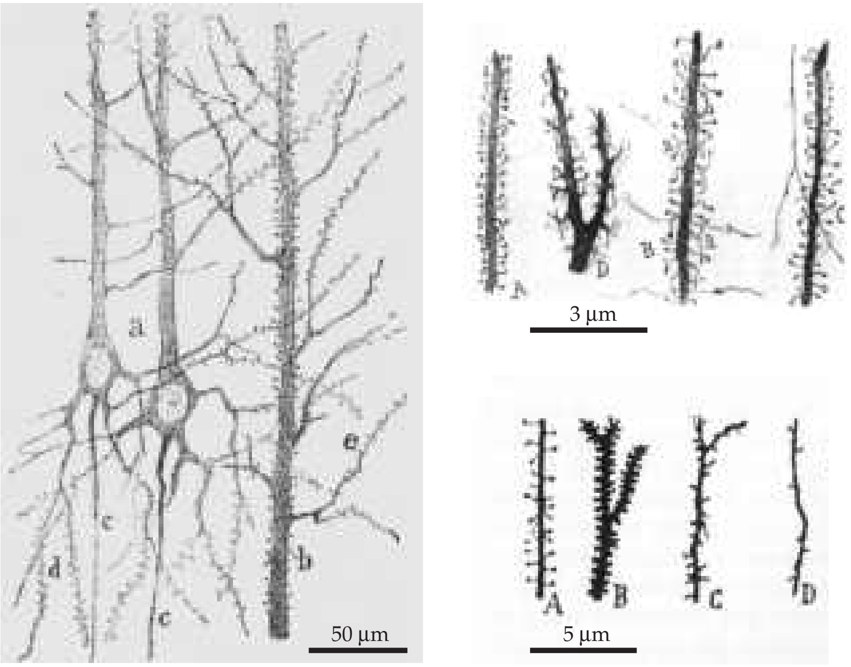
Many synapses in the brain involve small protrusions from dendritic branches known as spines (Figure A). Spines are distinguished by the presence of globular tips called spine heads; when spines are present, the synapses innervating dendrites are made from these heads. Spine heads are connected to the main shafts of dendrites by narrow links called spine necks (Figure B). Just beneath the site of contact between the terminals and the spine heads are intracellular structures called postsynaptic densities (Figure C). The number, size, and shape of dendritic spines are quite variable and can, at least in some cases, change dynamically over time (see Figure 24.14B).

Since the earliest description of these structures by Santiago Ramón y Cajal in the late 1800s, dendritic spines have fascinated generations of neuroscientists, inspiring many speculations about their function. One of the earliest conjectures was that the narrow spine neck electrically isolates synapses from the rest of the neuron. Given that the size of spine necks can change, such a mechanism could cause the physiological effect of individual synapses to vary over time, thereby providing a cellular mechanism for forms of synaptic plasticity such as LTP and LTD. However, subsequent measurements of the properties of spine necks indicate that these structures would be relatively ineffective in attenuating the flow of electrical current between spine heads and dendrites.

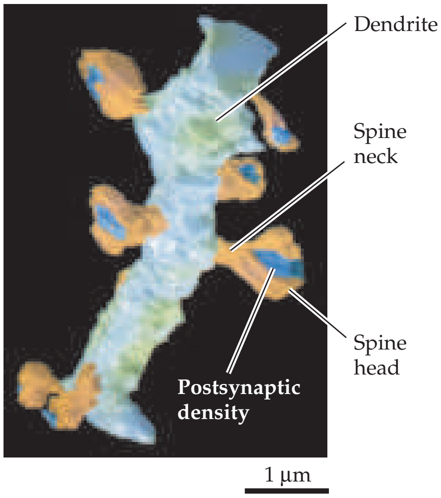
Another theory—currently the most popular functional concept—postulates that spines create biochemical compartments. This idea is based on the supposition that the spine neck could prevent diffusion of biochemical signals from the spine head to the rest of the dendrite. Several observations are consistent with this notion. First, measurements show that the spine neck does indeed serve as a barrier to diffusion, slowing the rate of molecular movement by a factor of 100 or more. Second, spines are found only at excitatory synapses, where it is known that synaptic transmission generates

(A) Cajal's classic drawings of dendritic spines. *Left*, Dendrites of cortical pyramidal neurons. *Right*, higher-magnification images of several different types of dendritic spines. (B) High-resolution electron microscopic reconstruction of a small region of the dendrite of a hippocampal pyramidal neuron. (C) Electron micrograph of a cross section through an excitatory synapse. (A from DeFelipe and Jones, 1988; B from Harris, 1994; C from Kennedy, 2000.)

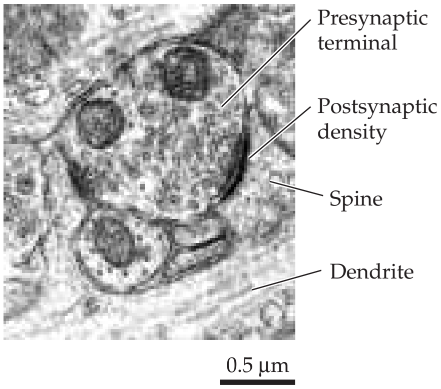
(A)



(B)



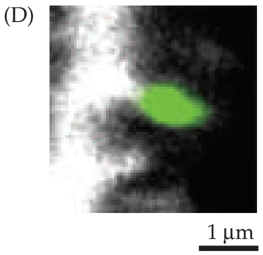
(C)

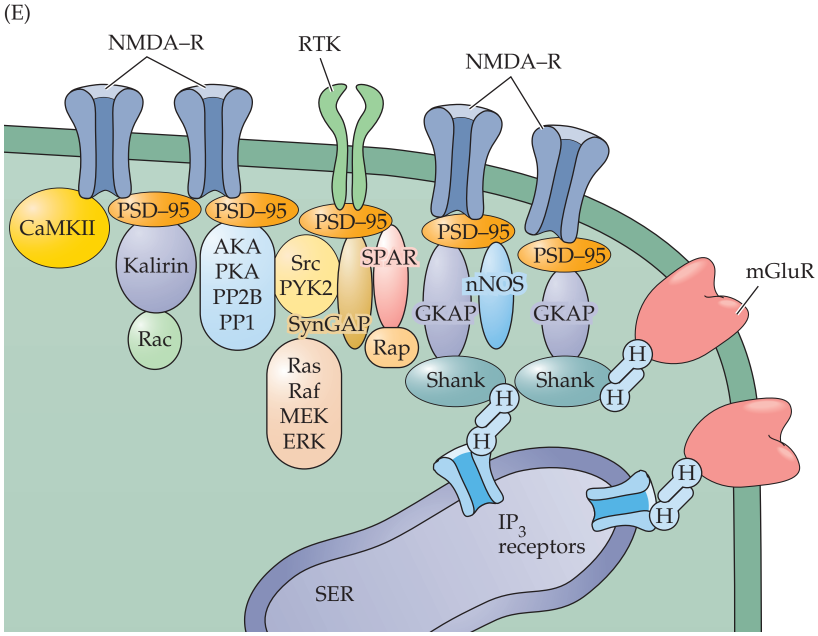


many diffusible signals, most notably the second messenger Ca^{2+}. Finally, fluorescence imaging shows that synaptic Ca^{2+} signals can indeed be restricted to dendritic spines (Figure D).

Nevertheless, there are counterarguments to the hypothesis that spines provide relatively isolated biochemical compartments. For example, it is known that other second messengers, such as IP_3, can diffuse out of the spine head and into the dendritic shaft. Presumably this difference in diffusion is due to the fact that IP_3 signals last longer than Ca^{2+} signals, allowing IP_3 sufficient time to overcome the diffusion barrier of the spine neck. Another relevant point is that postsynaptic Ca^{2+} signals are highly localized, even at excitatory synapses that do not have spines. Thus, in at least some instances, spines are neither necessary nor sufficient for localization of synaptic second messenger signaling.

A final and less controversial idea is that the purpose of spines is to serve as reservoirs where signaling proteins, such as the downstream molecular targets of Ca^{2+} and IP_3, can be concentrated. Consistent with this possibility, glutamate receptors are highly concentrated on spine heads, and the postsynaptic density comprises dozens of proteins involved in intracellular signal transduction (Figure E). According to this view, the spine head is the destination for these signaling molecules during the assembly of synapses, as well as the target of the second messengers that are produced by the local activation of glutamate receptors. Although the function of dendritic spines remains enigmatic, Cajal undoubtedly would be pleased at the enormous amount of attention that these tiny synaptic structures continue to command, and the real progress that has been made in understanding the variety of things they are capable of doing.





(D) Localized Ca^{2+} signal (green) produced in the spine of a hippocampal pyramidal neuron following activation of a glutamatergic synapse. (E) Postsynaptic densities include dozens of signal transduction molecules, including glutamate receptors (NMDA-R; mGluR), tyrosine kinase receptors (RTK), and many intracellular signal transduction molecules, most notably the protein kinase CaMKII. (D from Sabatini et al., 2002; E after Sheng and Kim, 2002.)

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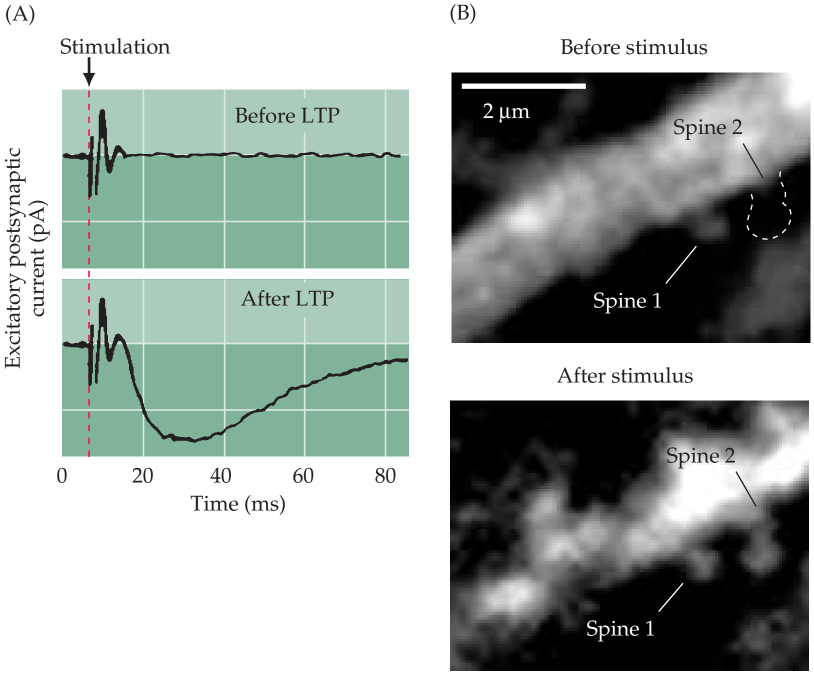


Figure 24.11 Insertion of postsynaptic AMPA receptors during LTP. (A) LTP induces AMPA receptor responses at silent synapses in the hippocampus. Prior to inducing LTP, no EPSCs are elicited at -65 mV at this silent synapse (upper trace). After LTP induction, the same stimulus produces EPSCs that are mediated by AMPA receptors (lower trace). (B) Distribution of fluorescently labeled AMPA receptor subunits (GluR1) before and 30 minutes after a high-frequency stimulus that can induce LTP. While the AMPA receptors of spine 1 did not change, there was a rapid delivery of AMPA receptors into spine 2 following the stimulus. (A after Liao et al., 1995; B from Shi et al., 1999.)

mediated by AMPA receptors at silent synapses (Figure 24.11A). Such rapid insertion of new AMPA receptors also can occur at "non-silent" excitatory synapses. Further, fluorescently tagged AMPA receptors can be seen to move into synapses under conditions that induce LTP (Figure 24.11B). Addition of these new AMPA receptors would be expected to increase the response of the postsynaptic cell to released glutamate, strengthening synaptic transmission as long as LTP is maintained. Under some circumstances, LTP also can cause a sustained increase in the ability of presynaptic terminals to release glutamate. Because LTP clearly is triggered by the actions of Ca^{2+} within the postsynaptic neuron (see Figure 24.10), this presynaptic potentiation requires that a retrograde signal (perhaps NO) spread from the postsynaptic region to the presynaptic terminals.

Long-Term Synaptic Depression

If synapses simply continued to increase in strength as a result of LTP, eventually they would reach some level of maximum efficacy, making it difficult to encode new information. Thus, to make synaptic strengthening useful, other processes must selectively weaken specific sets of synapses. Long-term depression (LTD) is such a process. In the late 1970s, LTD was found to occur at the synapses between the Schaffer collaterals and the CA1 pyramidal cells in the hippocampus. Whereas LTP at these synapses requires brief, high-frequency stimulation, LTD occurs when the Schaffer collaterals are stimulated at a low rate—about 1 Hz—for long periods (10–15 minutes). This pattern of activity depresses the EPSP for several hours and, like LTP, is specific to the activated synapses (Figure 24.12A,B). Moreover, LTD can erase the increase in EPSP size due to LTP, and, conversely, LTP can erase the decrease in EPSP size due to LTD. This complementarity suggests that LTD and LTP reversibly affect synaptic efficiency by acting at a common site.

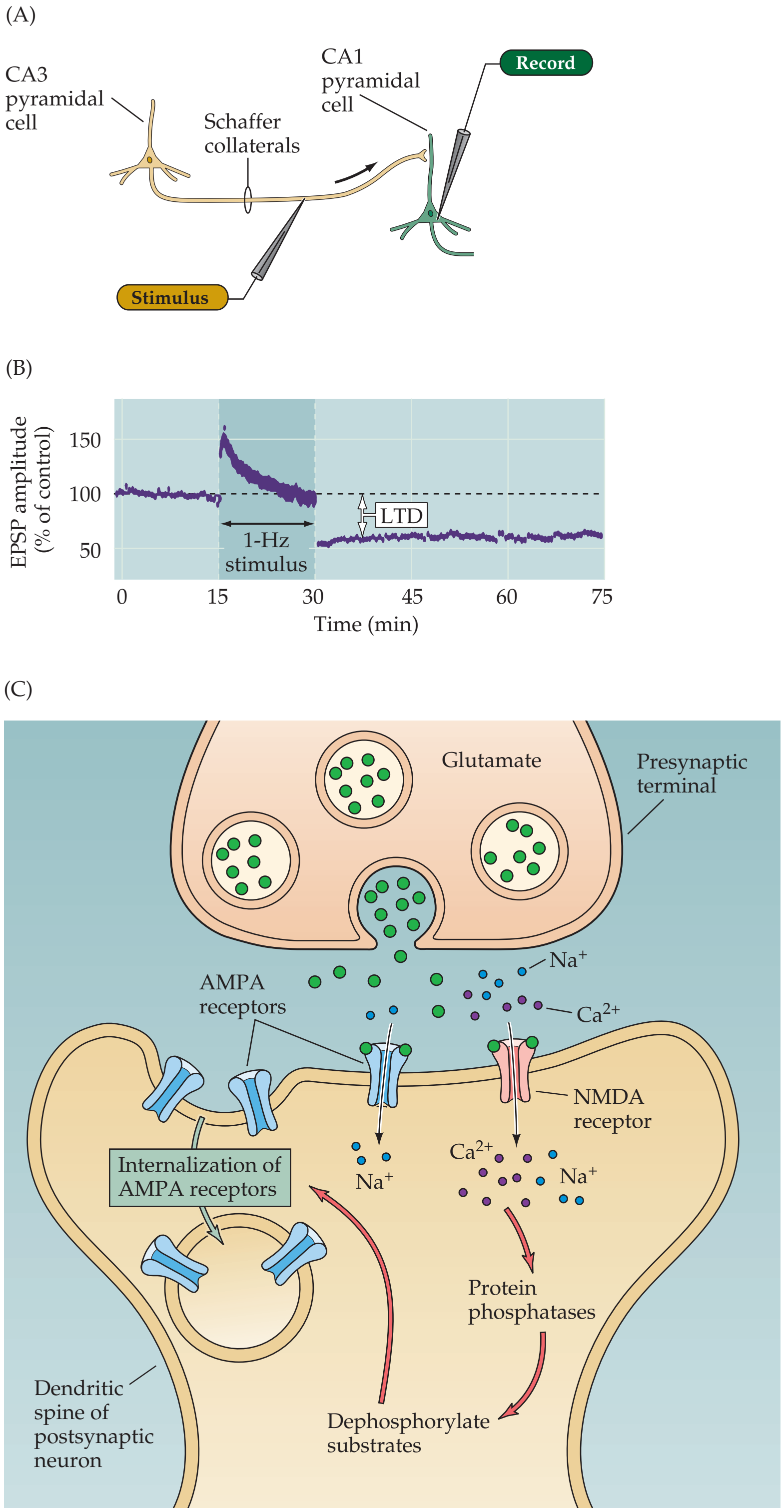
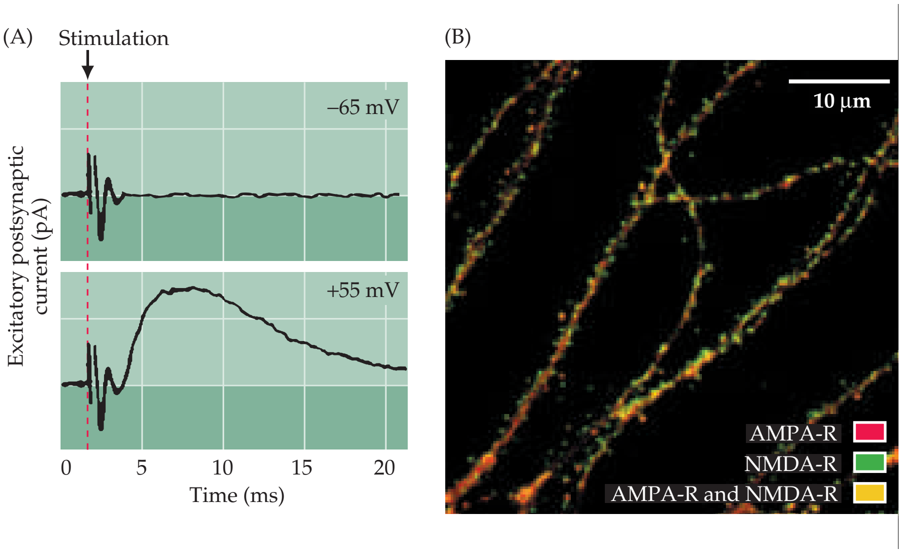

(A)
CA3 pyramidal cell
Schaffer collaterals
CA1 pyramidal cell
Record
Stimulus
(B)
EPSP amplitude (% of control)
150
100
50
LTD
1-Hz stimulus
0
15
30
45
60
75
Time (min)
(C)
Glutamate
Presynaptic terminal
Na+
AMPA receptors
Ca2+
NMDA receptor
Internalization of AMPA receptors
Na+
Ca2+
Na+
Protein phosphatases
Dendritic spine of postsynaptic neuron
Dephosphorylate substrates

Figure 24.12 Long-term synaptic depression in the hippocampus. (A) Electrophysiological procedures used to monitor transmission at the Schaffer collateral synapses on to CA1 pyramidal neurons. (B) Low-frequency stimulation (1 per second) of the Schaffer collateral axons causes a long-lasting depression of synaptic transmission. (C) Mechanisms underlying LTD. A low-amplitude rise in Ca^{2+} concencentration in the postsynaptic CA1 neuron activate postsynaptic protein phosphatases, which cause internalization of postsynaptic AMPA receptors, thereby decreasing the sensitivity to glutamate released from the Schaffer collateral terminals. (B after Mulkey et al., 1993.)

Box C

Silent Synapses



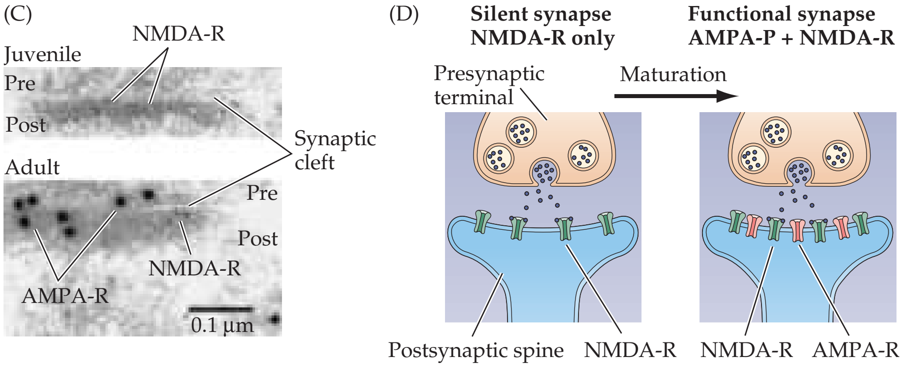
(A) Electrophysiological evidence for silent synapses. Stimulation of some axons fails to activate synapses when the postsynaptic cell is held at a negative potential (–65 mV, upper trace). However, when the postsynaptic cells is depolarized (+55 mV), stimulation produces a robust response (lower trace). (B) Immunofluorescent localization of NMDA receptors (green) and AMPA receptors (red) in a cultured hippocampal neuron. Many dendritic spines are positive for NMDA receptors but not AMPA receptors, indicating NMDA receptor-only synapses. (A after Liao et al., 1999; B courtesy of M. Ehlers.)

Several recent observations indicate that postsynaptic glutamate receptors are dynamically regulated at excitatory synapses. Early insight into this process came from the finding that stimulation of some glutamatergic synapses generates no postsynaptic electrical signal when the postsynaptic cell is at its normal resting membrane potential (Figure A). However, once the postsynaptic cell is depolarized, these "silent synapses" can transmit robust postsynaptic electrical responses. The fact that transmission at such synapses can be turned on or off in response to postsynaptic activity suggests an interesting and simple means of modifying neural circuitry.

Silent synapses are especially prevalent in development and have been found in many brain regions, including the hippocampus, cerebral cortex, and spinal cord. The silence of these synapses is evidently due to the voltage-dependent blockade of NMDA receptors by Mg^{2+} (see text and Chapter 6). At the normal resting membrane potential, presynaptic release of glutamate evokes no postsynaptic response at such synapses because their NMDA receptors are blocked by Mg^{2+}. However, depolarization of the postsynaptic neuron displaces the Mg^{2+}, allowing glutamate release to induce postsynaptic responses mediated by NMDA receptors.

Glutamate released at silent synapses evidently binds only to NMDA receptors. How, then, does glutamate release avoid activating AMPA receptors? One possibility is that glutamate released onto neighboring neurons diffuses to synapses on the neuron from which the electrical recording is being made. In this case, the diffusing glutamate may be present at concentrations sufficient to activate the high-affinity NMDA receptors, but not the low-affinity AMPA receptors. A second possibility is that a silent synapse has both AMPA and NMDA receptors, but its AMPA receptors are somehow not functional. Finally, some excitatory synapses may have only

LTP and LTD at the Schaffer collateral-CA1 synapses actually share several key elements. Both require activation of NMDA-type glutamate receptors and the resulting entry of Ca^{2+} into the postsynaptic cell. The major determinant of whether LTP or LTD arises appears to be the amount of Ca^{2+} in the postsynaptic cell: Small rises in Ca^{2+} lead to depression, whereas large increases trigger potentiation. As noted above, LTP is at least partially due to activation of CaMKII, which phosphorylates target proteins. LTD, on the other hand, appears to result from activation of Ca^{2+}-dependent phosphatases that cleave phosphate groups from these target molecules (see Chapter 7). Evidence in support of this idea is that phosphatase inhibitors prevent LTD, but have no effect on LTP. The different effects of Ca^{2+} during LTD and LTP may arise from the selective activation of protein phosphatases and kinases by low and high levels of Ca^{2+}. While the phosphatase substrates important for LTD have not yet been identified, it is possible that LTP



(C) Electron microscopy of excitatory synapses in CA1 stratum radiatum of the hippocampus from 10-day-old or 5-week-old (adult) rats double-labeled for AMPA receptors and NMDA receptors. The presynaptic terminal (pre), synaptic cleft, and postsynaptic spine (post) are indicated. AMPA receptors are abundant at the adult synapse, but absent from the younger synapse. (D) Diagram of glutamatergic synapse maturation. Early in postnatal development, many excitatory synapses contain only NMDA receptors. As synapses mature, AMPA receptors are recruited. (C from Petralia et al., 1999.)

NMDA receptors. Accumulating evidence supports the latter explanation. Most compelling are immunocytochemical experiments demonstrating the presence of excitatory synapses that have only NMDA receptors (green spots in Figure B). Such NMDA receptor-only synapses are particularly abundant early in postnatal development and decrease in adults (Figure C). Thus, at least some silent synapses are not a separate class of excitatory synapses that lack AMPA receptors, but rather an early stage in the ongoing maturation of the glutamatergic synapse (Figure D). Evidently, AMPA and NMDA receptors are not inextricably linked at excitatory synapses, but are targeted via independent cellular mechanisms. Such synapse-specific glutamate receptor composition implies sophisticated mechanisms for regulating the localization of each type of receptor. Dynamic changes in the trafficking of AMPA and NMDA receptors can strengthen or weaken synaptic transmission and are important in LTP and LTD, as well as in the maturation of glutamatergic synapses.

Although silent synapses have begun to whisper their secrets, much remains to be learned about their physiological importance and the molecular mechanisms that mediate rapid recruitment or removal of synaptic AMPA receptors.

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and LTD phosphorylate and dephosphorylate the same set of regulatory proteins to control the efficacy of transmission at the Schaeffer collateral-CA1 synapse. Just as LTP at this synapse is associated with insertion of AMPA receptors, LTD is often associated with a loss of synaptic AMPA receptors. This loss probably arises from internalization of AMPA receptors into the postsynaptic cell (Figure 24.12C), due to the same sort of clathrin-dependent endocytosis mechanisms important for synaptic vesicle recycling in the presynaptic terminal (see Chapter 5).

A somewhat different form of LTD is observed in the cerebellum (see Chapter 18). LTD of synaptic inputs onto cerebellar Purkinje cells was first described by Masao Ito and colleagues in Japan in the early 1980s. Purkinje neurons in the cerebellum receive two distinct types of excitatory input: climbing fibers and parallel fibers (Figure 24.13A; see Chapter 18). LTD reduces the strength of transmission at the parallel fiber synapse (Figure 24.13B) and has

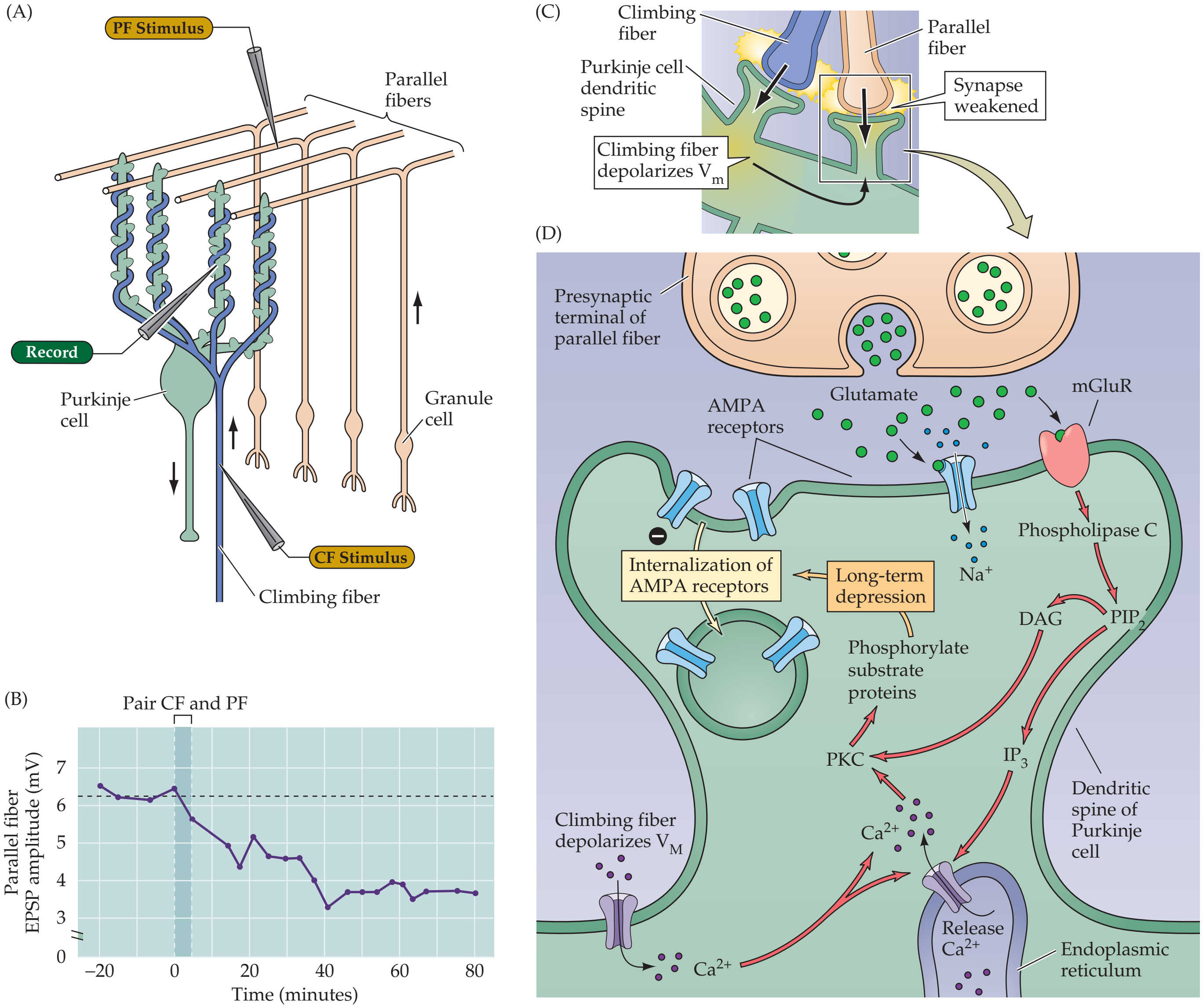

(A)
PF Stimulus
Parallel fibers
Record
Purkinje cell
Granule cell
CF Stimulus
Climbing fiber
(B)
Pair CF and PF
Parallel fiber EPSP amplitude (mV)
7
6
5
4
3
0
–20
0
20
40
60
80
Time (minutes)
(C)
Climbing fiber
Parallel fiber
Purkinje cell dendritic spine
Synapse weakened
Climbing fiber depolarizes V_m
(D)
Presynaptic terminal of parallel fiber
Glutamate
mGluR
AMPA receptors
Phospholipase C
Na^+
Internalization of AMPA receptors
Long-term depression
DAG
PIP_2
Phosphorylate substrate proteins
PKC
IP_3
Dendritic spine of Purkinje cell
Climbing fiber depolarizes V_M
Ca^{2+}
Release Ca^{2+}
Ca^{2+}
Endoplasmic reticulum

Figure 24.13 Long-term synaptic depression in the cerebellum. (A) Experimental arrangement. Synaptic responses were recorded from Purkinje cells following stimulation of parallel fibers and climbing fibers. (B) Pairing stimulation of climbing fibers (CF) and parallel fibers (PF) causes LTD that reduces the parallel fiber EPSP. (C) LTD requires depolarization of the Purkinje cell, produced by climbing fiber activation, as well as signals generated by active parallel fiber synapses. (D) Mechanism underlying cerebellar LTD. Glutamate released by parallel fibers activates both AMPA receptors and metabotropic glutamate receptors. The latter produces two second messengers, DAG and IP_3, which interact with Ca^{2+} that enters when climbing fiber activity opens voltage-gated Ca^{2+} channels. This leads to activation of PKC, which triggers clathrin-dependent internalization of postsynaptic AMPA receptors to weaken the parallel fiber synapse. (B after Sakurai, 1987.)

recently been found to depress transmission at the climbing fiber synapse as well. This form of LTD has been implicated in the motor learning that mediates the coordination, acquisition, and storage of complex movements within the cerebellum. Although the role of LTD in cerebellar motor learning remains controversial, it has nonetheless been a useful model system for understanding the cellular mechanisms of long-term synaptic plasticity.

Cerebellar LTD is associative in that it occurs only when climbing fibers and parallel fibers are activated at the same time (Figure 24.13C). The associativity arises from the combined actions of two distinct intracellular signal transduction pathways that are activated in the postsynaptic Purkinje cell due to the activity of climbing fiber and parallel fiber synapses. In the first pathway, glutamate released from the parallel fiber terminals activates at two types of receptors, the AMPA-type and metabotropic glutamate receptors (see Chapter 7). Glutamate binding to the AMPA receptor results in membrane depolarization, whereas binding to the metabotropic receptor produces the second messengers inositol trisphosphate (IP_3) and diacylglycerol (DAG) (see Chapter 7). The second signal transduction pathway, initiated by climbing fiber activation, causes a large influx of Ca^{2+} through voltage-gated channels and a subsequent increase in intracellular Ca^{2+} concentration. These second messengers work together to cause an amplified rise in intracellular Ca^{2+} concentration, due to IP_3 and Ca^{2+} triggering release of Ca^{2+} from IP_3-sensitive intracellular stores, and the synergistic activation of PKC by Ca^{2+} and DAG (Figure 24.13D). While the downstream substrate proteins that are phosphorylated by PKC are still be determined, it is known that the net effect is to cause an internalization of AMPA receptors via clathrin-dependent endocytosis (Figure 24.13D). This loss of AMPA receptors decreases the response of the postsynaptic Purkinje cell to glutamate release from the presynaptic terminals of the parallel fibers. Thus, in contrast to LTD in the hippocampus, cerebellar LTD requires the activity of a protein kinase, rather than a phosphatase, and does not involve Ca^{2+} entry through the NMDA type of glutamate receptor (which is not present in mature Purkinje cells). However, the net effect is the same in both cases: internalization of AMPA receptors is a common mechanism for decreased efficacy of both hippocampal and cerebellar synapses during LTD.

Changes in Gene Expression Cause Enduring Changes in Synaptic Function during LTP and LTD

The initial basis of long-lasting forms of synaptic plasticity in the mammalian CNS, such as LTP and LTD, entails post-translational changes that lead to altered distribution or density of postsynaptic AMPA receptors. Studies in *Aplysia*, however, showed that while a short-term form of serotonin-induced synaptic plasticity also has a post-translational origin, the long-term form of synaptic plasticity requires changes in gene expression (see Figure 24.4). This principle also appears to apply to long-lasting forms of synaptic plasticity in the mammalian CNS. Whereas hippocampal LTP has an early phase that involves post-translation mechanisms, it also has a later phase that depends on changes in gene expression and the synthesis of new proteins. Thus, blocking protein synthesis prevents LTP measured several hours after a stimulus but does not affect LTP measured at earlier times. This late phase of LTP is initiated by transcription factors such as CREB, which stimulate the expression of still other transcriptional regulators (Figure 24.14A). In addition, there is also evidence that the number and size of synaptic con-

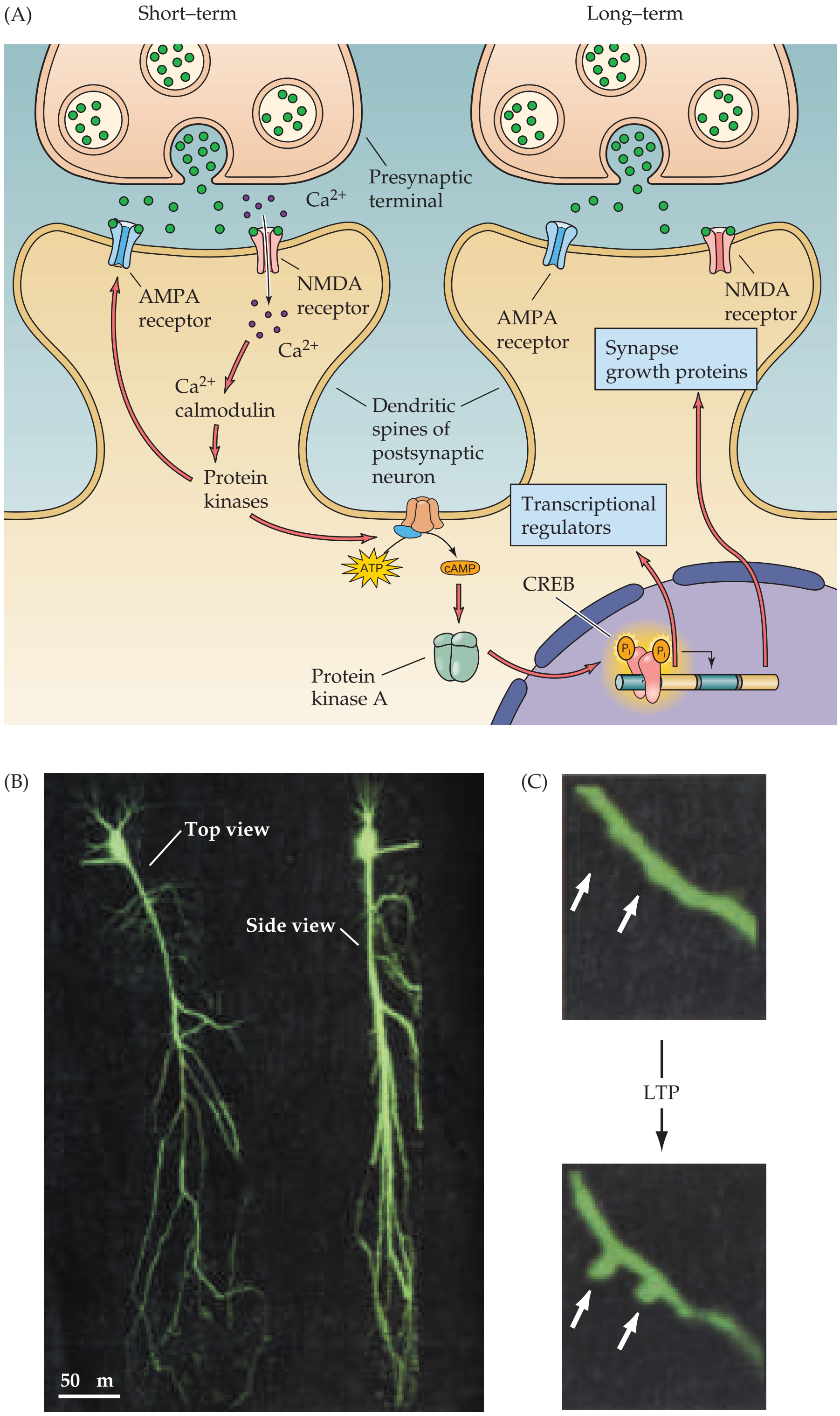

(A)
Short–term
Long–term
Presynaptic terminal
Ca^{2+}
AMPA receptor
NMDA receptor
Ca^{2+}
Ca^{2+} calmodulin
Protein kinases
Dendritic spines of postsynaptic neuron
ATP
cAMP
Protein kinase A
CREB
P_i
P_i
Transcriptional regulators
Synapse growth proteins
AMPA receptor
NMDA receptor
(B)
Top view
Side view
50 m
(C)
LTP

Figure 24.14 Mechanisms responsible for long-lasting changes in synaptic transmission during LTP. (A) The late component of LTP is due to PKA activating the transsciptional regulator CREB, which turns on expression of a number of genes that produce long-lasting changes in PKA activity and synapse structure. (B,C) Structural changes associated with LTP in the hippocampus. (B) The dendrites of a CA1 pyramidal neuron were visualized by filling the cell with a fluorescent dye. (C) New dendritic spines (white arrows) can be observed to appear approximately 1 hour after a stimulus that induces LTP. The presence of novel spines raises the possibility that LTP may arise, in part, from formation of new synapses. (A after Squire and Kandel, 1999; B and C after Engert and Bonhoeffer, 1999.)

tacts increases during LTP (Figure 24.14B,C). Thus, it is likely that some of the proteins newly synthesized during LTP are involved in construction of new synaptic contacts. While evidence for late components of hippocampal LTD is unclear, CREB may also be required for a late phase of LTD in the cerebellum.

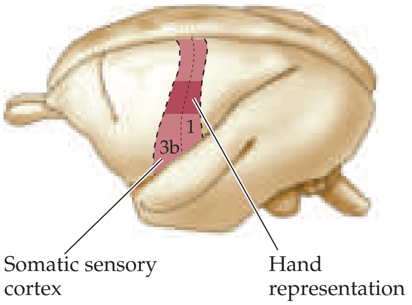
In summary, behavioral plasticity requires activity-dependent synaptic changes that lead to changes in the functional connections within and among neural circuits. These changes in the efficacy and local geometry of connectivity provide a basis not only for learning, memory, and other forms of plasticity, but also some pathologies. Thus, abnormal patterns of neuronal activity, such as those that occur in epilepsy, can stimulate abnormal changes in synaptic connections that may further increase the frequency and severity of seizures (Box D). Despite the substantial advances in understanding the cellular and molecular bases of some forms of plasticity, how selective changes of synaptic strength encode memories or other complex behavioral modifications in the mammalian brain is simply not known.

Plasticity in the Adult Cerebral Cortex

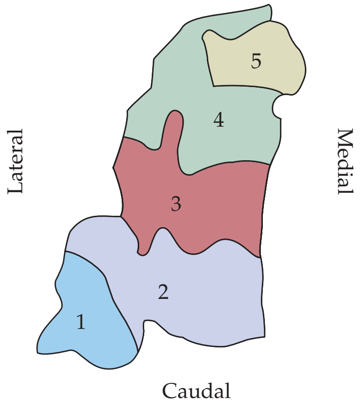
In addition to these cellular and molecular studies of synaptic plasticity, a good deal is now known about plasticity of adult cortical maps and of the receptive field properties of mature cortical neurons. Until the late 1970s, it was assumed that significant reorganization of cortical circuitry happened primarily during early postnatal development. This conclusion was based on the evidence for critical periods described in the preceding chapter, and on the relative permanence of neural deficits after CNS trauma in adults.

This view has to some extent been modified by evidence that topographic maps in the somatic sensory cortex of adult monkeys are actually capable of appreciable reorganization. As described in Chapter 8, the four cortical areas that define the primate somatic sensory cortex (Brodmann's areas 3a, 3b, 1, and 2) each contain a complete topographic representation of the body surface. Jon Kaas and Michael Merzenich took advantage of this arrangement by carefully defining the normal spatial organization of topographic maps in these regions. They then amputated a digit (or cut one of the nerves that innervate the hand) and reexamined topographical maps in the same animals several weeks later. Surprisingly, the somatic sensory cortex had changed: The cortical neurons that had been deprived of their normal peripheral input now responded to stimulation of other parts of the animal's hand (Figure 24.15). For example, if the third digit was amputated, cortical neurons that formerly responded to stimulation of digit 3 responded to stimulation of digits 2 or 4. Thus, the central representation of the remaining digits had expanded to take over the cortical territory that had lost its main input. Such "functional re-mapping" also occurs in the somatic sensory nuclei in the thalamus and brainstem; indeed, some of the reorganization of cortical circuits

(A) Owl monkey brain



(B) Normal hand representation



(C) Hand representation two months after digit 3 amputation

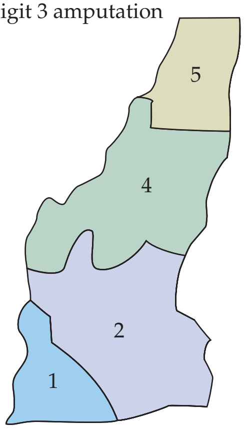


Figure 24.15 Functional changes in the somatic sensory cortex of an owl monkey following amputation of a digit. (A) Diagram of the somatic sensory cortex in the owl monkey, showing the approximate location of the hand representation. (B) The hand representation in the animal before amputation; the numbers correspond to different digits. (C) The cortical map determined in the same animal two months after amputation of digit 3. The map has changed substantially; neurons in the area formerly responding to stimulation of digit 3 now respond to stimulation of digits 2 and 4. (After Merzenich et al., 1984.)

Box D

Epilepsy: The Effect of Pathological Activity on Neural Circuitry

Epilepsy is a brain disorder characterized by periodic and unpredictable seizures mediated by the rhythmic firing of large groups of neurons. It seems likely that abnormal activity generates plastic changes in cortical circuitry that are critical to the pathogenesis of the disease.

The importance of neuronal plasticity in epilepsy is indicated most clearly by an animal model of seizure production called kindling. To induce kindling, a stimulating electrode is implanted in the brain, often in the amygdala (a component of the limbic system that makes and receives connections with the cortex, thalamus, and other limbic structures, including the hippocampus; see Chapter 28). At the beginning of such an experiment, weak electrical stimulation, in the form of a low-amplitude train of electrical pulses, has no discernible effect on the animal's behavior or on the pattern of electrical activity in the brain (laboratory rats or mice have typically been used for such studies). As this weak stimulation is repeated once a day for several weeks, it begins to produce behavioral and electrical indications of seizures. By the end of the experiment, the same weak stimulus that initially had no effect now causes full-blown seizures. This phenomenon is essentially permanent; even after an interval of a year, the same weak stimulus will again trigger a seizure. Thus, repetitive weak activation produces long-lasting changes in the excitability of the brain that time cannot reverse. The word *kindling* is therefore quite appropriate: A single match can start a devastating fire.

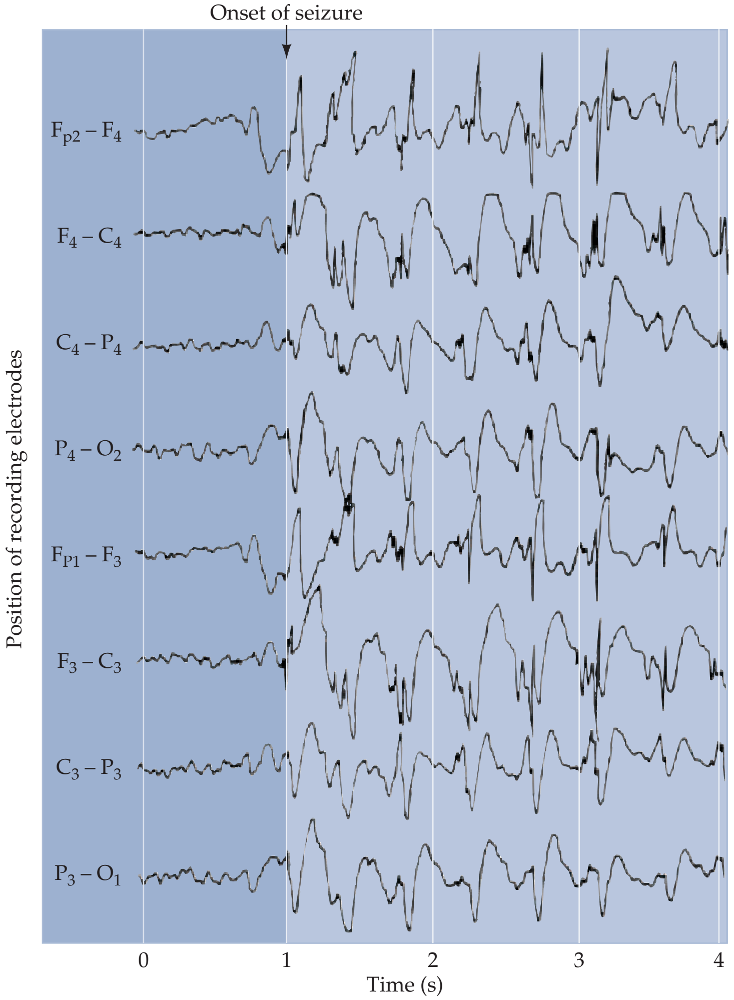
The changes in the electrical patterns of brain activity detected in kindled animals resemble those in human epilepsy. The behavioral manifestations of epileptic seizures in human patients range from mild twitching of an extremity to loss of consciousness and uncontrollable convulsions. Although many highly accomplished people have suffered from epilepsy (Alexander the Great, Julius Caesar, Napoleon, Dostoyevsky, and van Gogh, to name a few), seizures of sufficient intensity and frequency can obviously interfere with many aspects of daily life. Moreover, uncontrolled convulsions can lead to excitotoxicity (see Box D in Chapter 6). Up to 1% of the population is afflicted, making epilepsy one of the most common neurological problems.

Modern thinking about the causes (and possible cures) of epilepsy has focused on where seizures originate and the mechanisms that make the affected region hyperexcitable. Most of the evidence suggests that abnormal activity in small areas of the cerebral cortex (called foci) provide the triggers for a seizure that then spreads to other synaptically connected regions. For example, a seizure originating in the thumb area of the right motor cortex will first be evident as uncontrolled movement of the left thumb that subsequently extends to other more proximal limb muscles, whereas a seizure originating in the visual association cortex of the right hemisphere may be heralded by complex hallucinations in the left visual field. The behavioral manifestations of seizures therefore provide important clues for the neurologist seeking to pinpoint the abnormal region of cerebral cortex.

Epileptic seizures can be caused by a variety of acquired or congenital factors, including cortical damage from trauma, stroke, tumors, congenital cortical dysgenesis (failure of the cortex to grow properly), and congenital vascular malformations. One rare form of epilepsy, Rasmussen's encephalitis, is an autoimmune disease that arises when the immune system attacks the brain, using both humoral (i.e. antibodies) and cellular (lymphocytes and macrophages) agents that can destroy neurons. Some forms of epilepsy are heritable, and more than a dozen distinct genes have been demonstrated to underlie unusual types of epilepsy. However, most forms of familial epilepsy (such as juvenile myoclonic epilepsy and petit mal epilepsy) are caused by the simultaneous inheritance of more than one mutant gene.

may depend on this concurrent subcortical plasticity. This sort of adjustment in the somatic sensory system may contribute to the altered sensation of phantom limbs after amputation (see Box D in Chapter 9). Similar plastic changes now have been demonstrated in the visual, auditory, and motor cortices, suggesting that some ability to reorganize after peripheral deprivation or injury is a general property of the mature neocortex.

Appreciable changes in cortical representation also can occur in response to more physiological changes in sensory or motor experience. For instance, if a monkey is trained to use a specific digit for a particular task that is repeated many times, the functional representation of that digit determined



Electroencephalogram (EEG) recorded from a patient during a seizure. The traces show rhythmic activity that persisted much longer than the duration of this record. This abnormal pattern reflects the synchronous firing of large numbers of cortical neurons. (The designations are various positions of electrodes on the head; see Box C in Chapter 27 for additional information about EEG recordings.) (After Dyro, 1989.)

No effective prevention or cure exists for epilepsy. Pharmacological therapies that successfully inhibit seizures are based on two general strategies. One approach is to enhance the function of inhibitory synapses that use the neurotransmitter GABA; the other is to limit action potential firing by acting on voltage-gated Na^+ channels. Commonly used antiseizure medications include carbamazepine, phenobarbital, phenytoin (Dilantin®), and valproic acid. These agents, which must be taken daily, successfully inhibit seizures in 60–70% of patients. In a small fraction of patients, the epileptogenic region can be surgically excised. In extreme cases, physicians resort to cutting the corpus callosum to prevent the spread of seizures (most of the "split-brain" subjects described in Chapter 26 were patients suffering from intractable epilepsy). One of the major reasons for controlling epileptic activity is to prevent the more permanent plastic changes that would ensue as a consequence of abnormal and excessive neural activity.

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by electrophysiological mapping can expand at the expense of the other digits (Figure 24.16). In fact, significant changes in receptive fields of somatic sensory neurons can be detected when a peripheral nerve is blocked temporarily by a local anesthetic. The transient loss of sensory input from a small area of skin induces a reversible reorganization of the receptive fields of both cortical and subcortical neurons. During this period, the neurons assume new receptive fields that respond to tactile stimulation of the skin surrounding the anesthetized region. Once the effects of the local anesthetic subside, the receptive fields of cortical and subcortical neurons return to their usual size. The common experience of an anesthetized area of skin feel-

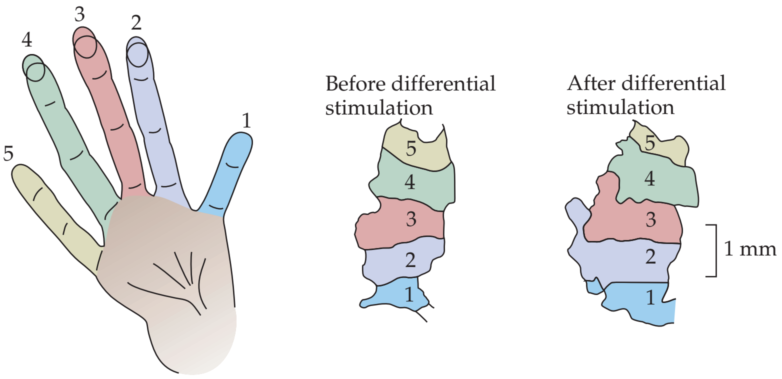

4
3
2
1
5
Before differential stimulation
5
4
3
2
1
After differential stimulation
5
4
3
2
1
1 mm

Figure 24.16 Functional expansion of a cortical representation by a repetitive behavioral task. An owl monkey was trained in a task that required heavy usage of digits 2, 3, and occasionally 4. The map of the digits in the primary somatic sensory cortex prior to training is shown. After several months of "practice," a larger region of the cortex contained neurons activated by the digits used in the task. Note that the specific arrangements of the digit representations are somewhat different from the monkey shown in Figure 24.14, indicating the variability of the cortical representation in particular animals. (After Jenkins et al., 1990.)

ing disproportionately large—following dental anesthesia—may be a consequence of this temporary change.

Despite these intriguing observations, the mechanism, purpose, and significance of the reorganization of sensory and motor maps that occurs in adult cortex are not known. Clearly, limited changes in cortical circuitry can occur in the adult brain, even though the basic features of cortical organization—such as ocular dominance columns and the broader topographical organization of inputs from the thalamus—remain fixed (see Chapter 23). If a greater degree of cortical plasticity were possible, recovery from brain injury would be far more vigorous and effective than centuries of clinical observation have shown it to be. Given their rapid and reversible character, most of these changes in cortical function probably reflect alterations in the strength of synapses already present.

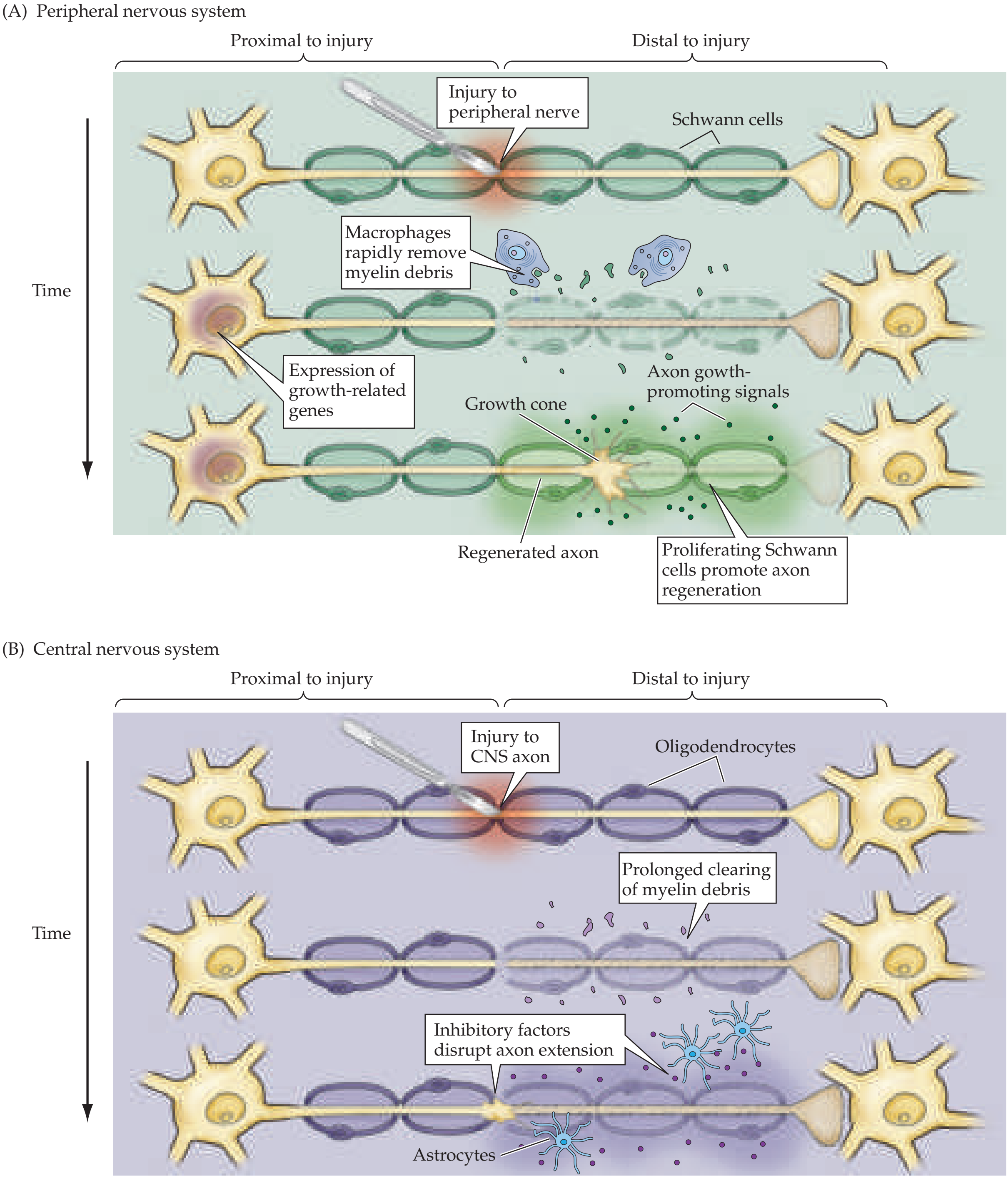
Recovery from Neural Injury

These various observations on adult plasticity indicate that normal experience can alter the strength of existing synapses and even elicit some local remodeling of synapses and circuits. More extensive growth and remodeling are stimulated by nervous system injury. As just noted, however, this remodeling rarely results in full restoration of lost function.

Traumatic injury, interruption of blood supply, and degenerative diseases all can damage axons in peripheral nerves, or neuronal cell bodies and syn-

Figure 24.17 Different responses to injury in the peripheral (A) and central (B) nervous systems. Damage to a peripheral nerve leads to series of cellular responses, collectively called Wallerian degeneration (after Augustus Waller, the nineteenth century English physician who first described these phenomena). *Distal* to the site of injury, axons disconnected from their cell bodies degenerate, and invading macrophages remove the cellular debris. Schwann cells that formerly ensheathed the axons proliferate, align to form longitudinal arrays, and increase their production of neurotrophic factors that can promote axon regeneration. Schwann cell surfaces and the extracellular matrix also provide a favorable substratum for the extension of regenerating axons. In the CNS, the removal of myelin debris is relatively slow, and the myelin membranes produce inhibitory molecules that can block axon growth (see Chapter 23). Astrocytes at the site of injury also interfere with regeneration. *Proximal* to the injury, neuron cell bodies react to peripheral nerve injury by inducing expression of growth-related genes, including those for major components of axonal growth cones. Following CNS injury, however, neurons typically fail to activate these growth-associated genes. ▶

apses in the more complex circuitry of the brain or spinal cord. When peripheral nerves are injured, the damaged axons regenerate vigorously and can re-grow over distances of many centimeters or more. Under favorable circumstances, these regenerated axons can also reestablish synaptic connections with their targets in the periphery. In contrast, CNS axons typically fail to regenerate (Figure 24.17). As a result, axonal damage in the retina, spinal cord, or the rest of the brain leads to permanent blindness, paralysis, and other disabilities. What, then, explains this difference in the regeneration of


(A) Peripheral nervous system
Proximal to injury
Distal to injury
Injury to peripheral nerve
Schwann cells
Time
Macrophages rapidly remove myelin debris
Expression of growth-related genes
Axon gowth-promoting signals
Growth cone
Regenerated axon
Proliferating Schwann cells promote axon regeneration
(B) Central nervous system
Proximal to injury
Distal to injury
Injury to CNS axon
Oligodendrocytes
Time
Prolonged clearing of myelin debris
Inhibitory factors disrupt axon extension
Astrocytes

peripheral nerves compared to axonal regeneration in the brain or spinal cord?

Successful regeneration in peripheral nerves depends on two critical conditions. First, the injured neuron must respond to axon interruption by initiating a program of gene expression that can support axon elongation. Many of the genes involved in the outgrowth of axons over comparatively short distances during embryonic development (see Chapter 23) are not normally expressed in adult neurons. Interruption of axons reactivates expression of some of these genes in the peripheral nervous system, but not in the adult CNS. Axons damaged in the long tracts of the brain or spinal cord, particularly at sites far from their cell bodies, rarely re-express these genes. Second, once a damaged neuron initiates a genetic program that can support axon regrowth, the emerging growth cones must encounter an environment that can support and guide the regrowing axons. In peripheral nerves, damage or degeneration triggers changes that produce a favorable environment for axon elongation. Schwann cells and other non-neuronal cells respond to axonal injury by elaborating cell adhesion molecules, extracellular matrix components, and an array of neurotrophins and other signals that promote axon growth (see Chapter 22). Equally important, damaged peripheral nerves are invaded by macrophages that rapidly remove fragments of degenerating axons and myelin that might otherwise inhibit the growth of regenerating axons.

In contrast, damage to axonal tracts in the adult CNS triggers a very different set of changes. First, the relative distances for specific growth are far longer than they were in the developing brain and spinal cord. Moreover, as axons and their myelin sheaths break down, the remnants are not cleared efficiently and can persist for many weeks, posing a substantial impediment to regeneration. This inhibition appears to reflect the activity of inhibitory signals produced by glia and other cells at the site of injury, including a protein called Nogo that blocks axon extension by interacting with advancing growth cones (see Chapter 22). Nogo is produced primarily by oligodendrocytes, the glia that normally form myelin sheaths around CNS axons. The contributions of Nogo to axon regeneration remains unclear. Blocking its function with specific antibodies can enhance growth of axons in the mature injured CNS; however, genetic inactivation of Nogo (or its receptor) in mice does not result in significantly enhanced axon regeneration in the CNS following injury.

To make matters worse, astrocytes reacting to CNS injury express additional inhibitors of axon extension, and the cytokines released by microglia or macrophages as part of the inflammatory response to injury also diminish axon growth. As a consequence, even if a central neuron initiates a genetic program for regeneration, growth cones emerging from the site of a lesion in the adult CNS encounter an array of circumstances that impede continued growth and reestablishment of connections.

The contributions of the intrinsic capacity for growth in mature CNS neurons versus the local axonal environment in CNS regeneration was explored in detail by Albert Aguayo and his co-workers at McGill University in the 1980s. They grafted segments of peripheral nerve into sites in the CNS, such as optic nerve, spinal cord, or other locations, and then determined whether neurons were able to regenerate axons through the peripheral grafts. Their studies showed that at least some CNS axons are able to take advantage of the more supportive growth environment of the peripheral nerve, regenerating over distances of many centimeters and in some cases restoring appropriate synaptic connections (Box E).

This demonstration that CNS axons can sometimes regenerate successfully into a peripheral nerve graft sparked intensive efforts by many labs to produce a similarly supportive environment for axon growth within the long tracts of the brain or spinal cord. For example, Martin Schwab and his collaborators showed that implanting cells engineered to secrete antibodies against inhibitory proteins, including Nogo, alleviated some of the inhibitory properties of CNS myelin and other cells at the site of axon injury in experimental animals. Another approach was to introduce cells that provide a more supportive environment for regenerating axons in the damaged CNS. Schwann cells, neural stem cells (see next section), and specialized glial cells from the olfactory nerve all can be grown in tissue culture and introduced into the brains or spinal cords of experimental animals, where they modestly improve axon regrowth and, in some cases, may contribute to limited functional recovery.

In short, regeneration in adults is held in check by ongoing suppression of genes required for effective axon elongation. Injury to the peripheral nervous system readily induces expression of this genetic program, while interruption of mammalian CNS axons does not. Once CNS neurons have activated these genes, in principle regrowth could be enhanced by removal or neutralization of inhibitory molecules, minimizing local inflammatory responses, and by the introduction of cells that provide a more supportive growth environment. These strategies, however, have not been proven clinically useful, and functional loss after brain and spinal cord injury remains a daunting clinical challenge.

Generation of Neurons in the Adult Brain

It has long been known that mature, differentiated neurons do not divide (see Chapter 21). It does not follow, however, that *all* the neurons in the adult brain are produced during embryonic development, even though this interpretation has generally been assumed. The merits of this assumption were initially challenged in the 1960s, in experiments indicating that interneurons in a variety of brain regions could be labeled with tritiated thymidine injected in the adult, rather than during early development. This finding suggested that some interneurons—particularly in the olfactory bulb and hippocampus—are generated in the mature rather than in the developing animal. Moreover, a variety of experiments in fish, frogs, and birds indicated a limited generation of new neurons throughout life in these species, especially in animals (like goldfish) where there is significant continuing growth of the entire organism throughout the course of its life. In songbirds, new neurons are able to extend dendrites, generate synaptic and action potentials, and project long axons to establish appropriate connections with other brain nuclei. Production of new neurons is apparent in many parts of the birds' brains, but seems especially prominent in areas involved in song production (see Box B in Chapter 23). These observations showed that the adult brain can generate at least some new nerve cells and incorporate them into neural circuits (see also Chapter 14).

The production of new neurons in the mammalian adult brain has now been examined (or re-examined) in mice, rats, monkeys, and humans. In all these cases, new nerve cells in the CNS have been restricted to just two regions of the brain: (1) The granule cell layer of the olfactory bulb; and (2) the dentate gyrus of the hippocampus (Figure 24.18). Furthermore, the new nerve cells are primarily local circuit neurons or interneurons. New neurons

Box E

Why Aren't We More Like Fish and Frogs?

The central nervous system of adult mammals, including humans, recovers only poorly from injury. As indicated in the text, once severed, major axon tracts (such as those in the spinal cord) never regenerate. The devastating consequences of these injuries—e.g., loss of movement and the inability to control basic bodily functions—has led many neuroscientists to seek ways of restoring the connections of severed axons. There is no a priori reason for this biological failure, since "lower" vertebrates—e.g., lampreys, fish, and frogs—*can* regenerate a severed spinal cord or optic nerve. Even in mammals, the inability to regenerate axonal tracts is a special failing of the central nervous system; peripheral nerves can and do regenerate in adult animals, including humans. Why, then, not the central nervous system?

At least a part of the answer to this puzzle apparently lies in the molecular cues that promote and inhibit axon outgrowth. In mammalian peripheral nerves, axons are surrounded by a basement membrane (a proteinaceous extracellular layer composed of collagens, glycoproteins, and proteoglycans) secreted in part by Schwann cells, the glial cells associated with peripheral axons. After a peripheral nerve is crushed, the axons within it degenerate; the basement membrane around each axon, however, persists for months. One of the major components of the basement membrane is laminin, which (along with other growth-promoting molecules in the basement membrane) forms a hospitable environment for regenerating growth cones. The surrounding Schwann cells also react by releasing neurotrophic factors, which further promote axon elongation (see text). This peripheral environment is so favorable to regrowth that even neurons from the central nervous system can be induced to extend into transplanted segments of peripheral nerve. Albert Aguayo and his colleagues at the Montreal General Hospital found that grafts derived from peripheral nerves can act as "bridges" for central neurons (in this case, retinal ganglion cells), allowing them to grow for over a centimeter (Figure A); they even form a few functional synapses in their target tissues (Figure B).

These several observations suggest that the failure of central neurons to regenerate is not due to an intrinsic inability to sprout new axons, but rather to something in the local environment that prevents growth cones from extending. This impediment could be the absence of growth-promoting factors—such as the neurotrophins—or the presence of molecules that actively prevent axon outgrowth. Studies by Martin Schwab and his colleagues point to the latter possibility. Schwab found that central nervous system myelin contains an inhibitory component that causes growth cone collapse in vitro and prevents axon growth in vivo. This component, recognized by a monoclonal antibody called IN-1, is found in the myelinated portions of the central nervous system but is absent from peripheral nerves. IN-1 also recognizes molecules in the optic nerve and spinal cord of mammals, but is missing in the same sites in fish, which do regenerate these central tracts. Nogo-A, the primary antigen recognized by the IN-1 antibody, is secreted by oligodendrocytes, but not by Schwann cells in the peripheral nervous system. Most dramatically, the IN-1 antibody increases the extent of spinal cord regeneration when provided at the site of injury in rats with spinal cord damage. All this implies that the human central nervous system differs from that of many "lower" vertebrates in that humans and other mammals present an unfavorable molecular environment for regrowth after injury. Why this state of affairs occurs is not known. One speculation is that the extraordinary amount of information stored in mammalian brains puts a premium on a stable pattern of adult connectivity.

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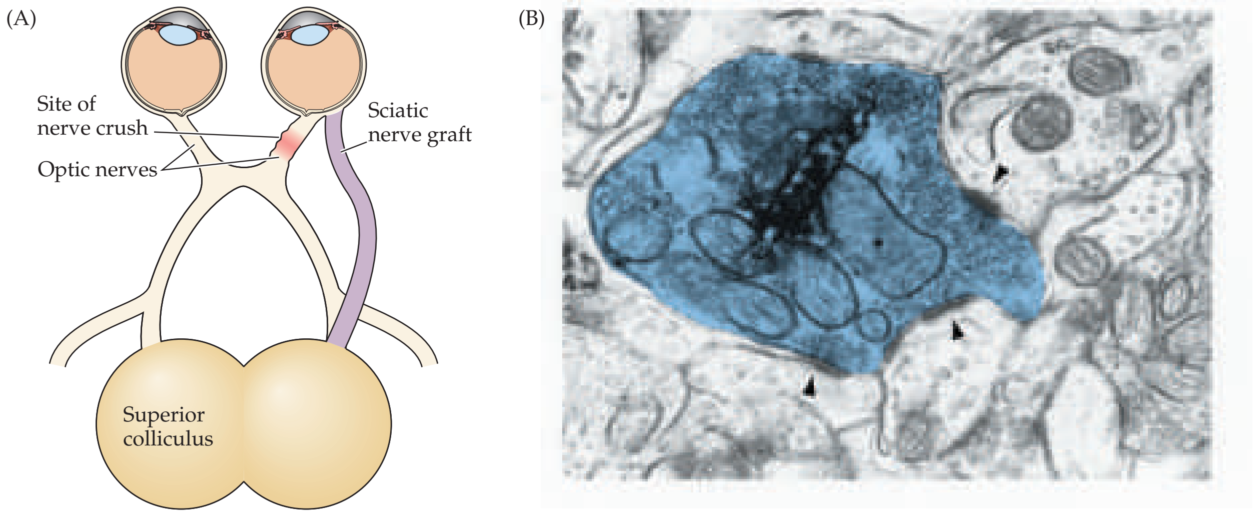
with long distance projections have not been observed. Each of these populations in the olfactory bulb and hippocampus is apparently generated from nearby sites near the surface of the lateral ventricle. At least some of these new nerve cells become integrated into functional synaptic circuits. Evidently, a limited production of new neurons occurs continually in just a few specific loci. The ultimate functional significance for the addition of such cells in mammals or other animals remains unknown.

If differentialted neurons cannot divide (see Chapter 21), how does the adult brain generate these nerve cells? The answer emerged with the discovery that the subventricular zone (a population of cells adjacent to the ventricular space found in the cortical hemispheres and hippocampus that pro-



Implantation of a section of peripheral nerve into the central nervous system facilitates the extension of central axons. (A) Mammalian retinal ganglion neurons, which do not normally regenerate following a crush injury, will grow for many millimeters into a graft derived from the sciatic nerve. (B) If the distal end of the graft is inserted into a normal target of retinal ganglion cells, such as the superior colliculus, a few regenerating axons invade the target and form functional synapses, as shown in this electron micrograph (arrowheads). The dark material is an intracellularly transported label that identifies particular synaptic terminals as originating from a regenerated retinal axon. (A after So and Aguayo, 1985; B from Bray et al., 1991.)

At present there is only one modestly helpful treatment for CNS injuries such as spinal cord transection. High doses of a steroid, methylprednisolone, immediately after the injury prevents some of the secondary damage to neurons resulting from the initial trauma. Although it may never be possible to fully restore function after such injuries, enhancing axon regeneration, blocking inhibitory molecules and providing additional trophic support to surviving neurons could in principle allow sufficient recovery of motor control to give afflicted individuals a better quality of life than they now enjoy. The best “treatment,” however, is to prevent such injuries from occurring, since there is now very little that can be done after the fact.

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duces neurons during development) retains some **neural stem cells** in the adult. The term “stem cells” refers to a population of cells that are self-renewing—each cell can divide symmetrically to give rise to more cells like itself, but also can divide asymmetrically, giving rise to a new stem cell plus one or more differentiated cells. Thus a neural stem cell can give rise to the full complement of basic cell classes found in neural tissue—i.e., neurons, astrocytes, and oligodendroglia (see Box A in Chapter 21), as well as more stem cells. Adult stem cells can be isolated not only from the anterior subventricular zone (near the olfactory bulb) and dentate gyrus, but from many other parts of the forebrain, cerebellum, midbrain, and spinal cord, although they do not apparently produce any new neurons in these sites.

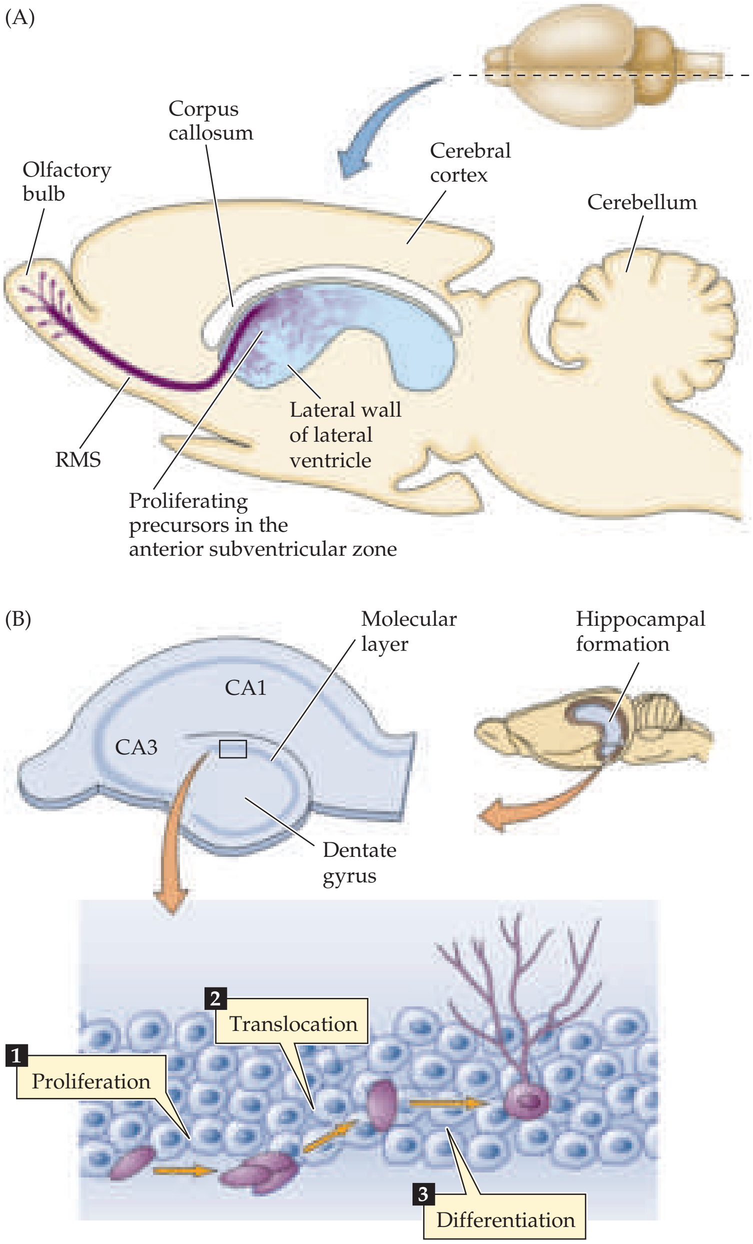

Figure 24.18 Neurogenesis in the adult mammalian brain. (A) Neural precursors in the epithelial lining of the anterior lateral ventricles in the forebrain (a region called the anterior subventricular zone, or SVZ) give rise to postmitotic neuroblasts that migrate to the olfactory bulb via a distinctive pathway known as the rostral migratory stream or RMS. Neuroblasts that migrate to the bulb via the RMS become either olfactory bulb granule cells or periglomerular cells; both cell types function as interneurons in the bulb. (B) In the mature hippocampus, a population of neural precursors is resident in the basal aspect of the granule cell layer of the dentate gyrus. These precursors give rise to postmitotic neuroblasts that translocate from the basal aspect of the granule cell layer to more apical levels. In addition, some of these neuroblasts elaborate dendrites and a local axonal process and apparently become GABAergic interneurons within the dentate gyrus. (After Gage, 2000.)

(A)
Corpus callosum
Olfactory bulb
Cerebral cortex
Cerebellum
RMS
Lateral wall of lateral ventricle
Proliferating precursors in the anterior subventricular zone
(B)
Molecular layer
Hippocampal formation
CA1
CA3
Dentate gyrus
2 Translocation
1 Proliferation
3 Differentiation

Why the generation of neurons is so restricted in the adult brain is not understood. Nevertheless, the fact that new neurons can be generated in at least a few regions of the adult brain shows that this phenomenon can occur in the adult CNS. The ability of newly generated neurons to integrate into some synaptic circuits adds to the available mechanisms for plasticity in the adult brain. Thus, many investigators have begun to explore the potential use of stem cells for the repair of circuits damaged by traumatic injury or degenerative disease.

Summary

The adult nervous system exhibits plastic change in a variety of circumstances. Studies of behavioral plasticity in several invertebrates and of the neuromuscular junction suggest that modification of synaptic strength is responsible for much of the ongoing change in synaptic function in adults. Synapses exhibit many forms of plasticity that occur over a broad temporal range. At the shortest times (seconds to minutes), facilitation, post-tetanic potentiation, and depression provide rapid but transient modifications based on alterations in Ca^{2+} signaling and synaptic vesicle pools at recently active synapses. Longer-lasting forms of synaptic plasticity such as LTP and LTD are also based on Ca^{2+} and other intracellular second messengers. In these more enduring forms of plasticity, protein phosphorylation and changes in gene expression greatly outlast the period of synaptic activity and can yield persistent changes in synaptic strength (hours to days or longer). Different brain regions evidently use one or more of these strategies to learn new behaviors and acquire new memories. Neuronal damage can also induce plastic changes. Peripheral neurons can regenerate axons following damage, though the capacity of CNS axons to regenerate is severely limited. In addition, neural stem cells are present in certain regions of the adult brain, allowing the production of some new neurons in a few brain regions. These various forms of adult plasticity can modify the function of the mature brain and provide some hope for improving the limited ability of the CNS to recover successfully from trauma and neurological disease.

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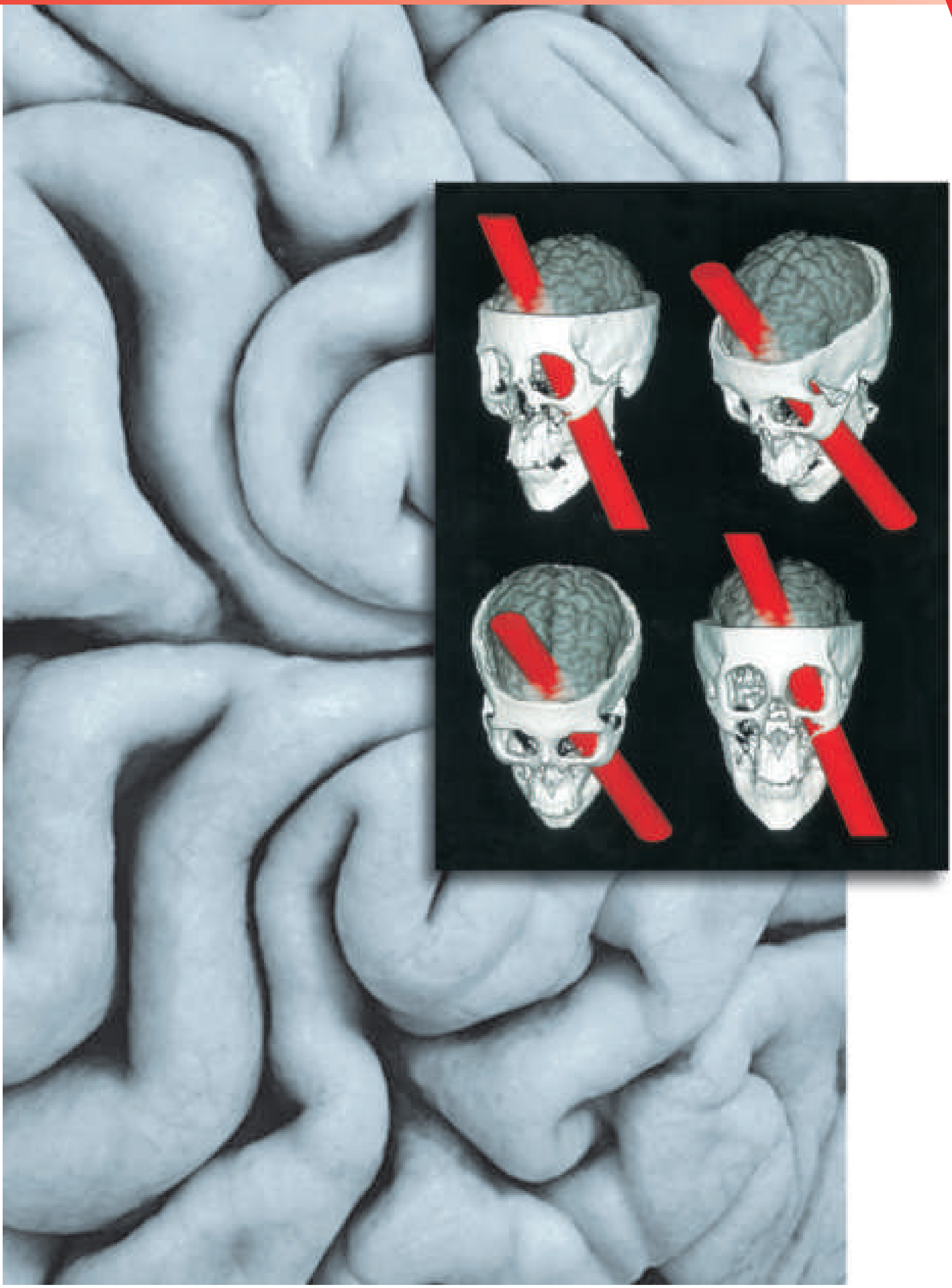
Complex Brain Functions

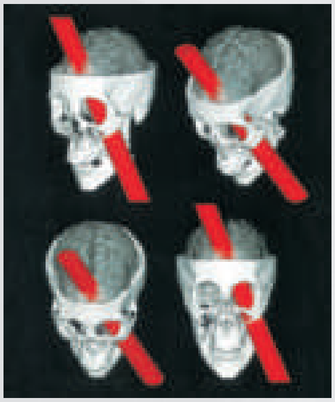
V



UNIT V

COMPLEX BRAIN FUNCTIONS

25 The Association Cortices
26 Language and Speech
27 Sleep and Wakefulness
28 Emotions
29 Sex, Sexuality, and the Brain
30 Memory



The function of the frontal cortex was first suggested by a dramatic accident that occurred in 1848. An explosion drove a tamping rod through the frontal part of the brain of a railroad worker named Phineas P. Gage. Remarkably, Gage survived, and his subsequent behavioral deficits stimulated much thinking about complex brain functions. The illustration here is a reconstruction of the trajectory of the rod based on Gage's skull, which is housed in the Warren Museum at Harvard Medical School. (Courtesy of H. Damasio.)

The awareness of physical and social circumstances, the ability to have thoughts and feelings (emotions), to be sexually attracted to others, to express these things to our fellow humans by language, and to store such information in memory certainly rank among the most intriguing functions of the human brain. Given their importance in daily life—and for human culture generally—it is not surprising that much of the human brain is devoted to these and other complex mental functions. The intrinsic interest of these aspects of human behavior is unfortunately equaled by the difficulty—both technical and conceptual—involved in unraveling their neurobiological underpinnings. Nonetheless, a good deal of progress has been made in deciphering the structural and functional organization of the relevant brain regions. Especially important has been the steady accumulation of case studies during the last century or more that, by the signs and symptoms resulting from damage to specific brain regions, have indicated much about the primary location of various complex brain functions. More recently, the advent of noninvasive brain imaging techniques has provided a much deeper understanding of some of these abilities in normal human subjects as well as in neurological patients. Finally, complementary electrophysiological experiments in nonhuman primates and other experimental animals have begun to elucidate the cellular correlates of many of these functions. Taken together, these observations have established a rapidly growing body of knowledge about these more complex aspects of the human brain. This general domain of investigation has come to be called "cognitive neuroscience," a field that promises to loom ever larger in the new century.

Chapter 25

The Association Cortices

Overview

The association cortices include most of the cerebral surface of the human brain and are largely responsible for the complex processing that goes on between the arrival of input in the primary sensory cortices and the generation of behavior. The diverse functions of the association cortices are loosely referred to as *cognition*, which literally means the process by which we come to know the world. ("Cognition" is perhaps not the best word to indicate this wide range of neural functions, but it has become part of the working vocabulary of neurologists and neuroscientists.) More specifically, cognition refers to the ability to attend to external stimuli or internal motivation; to identify the significance of such stimuli; and to make meaningful responses. Given the complexity of these tasks, it is not surprising that the association cortices receive and integrate information from a variety of sources, and that they influence a broad range of cortical and subcortical targets. Inputs to the association cortices include projections from the primary and secondary sensory and motor cortices, the thalamus, and the brainstem. Outputs from the association cortices reach the hippocampus, the basal ganglia and cerebellum, the thalamus, and other association cortices. Insight into the function of these cortical regions has come primarily from observations of human patients with damage to one or another of these areas. Noninvasive brain imaging of normal subjects, functional mapping at neurosurgery, and electrophysiological analysis of comparable brain regions in non-human primates have generally confirmed clinical deductions. Together, these studies indicate that, among other functions, the parietal association cortex is especially important for attending to stimuli in the external and internal environment, that the temporal association cortex is especially important for identifying the nature of such stimuli, and that the frontal association cortex is especially important for planning appropriate behavioral responses.

The Association Cortices

The preceding chapters have considered in some detail the parts of the brain responsible for encoding sensory information and commanding movements (i.e., the primary sensory and motor cortices). But these regions account for only a fraction (perhaps a fifth) of the cerebral cortex (Figure 25.1). The consensus has long been that much of the remaining cortex is concerned with attending to complex stimuli, identifying the relevant features of such stimuli, recognizing the related objects, and planning appropriate responses (as well as storing aspects of this information). Collectively, these integrative abilities are referred to as **cognition**, and it is evidently the association cor-

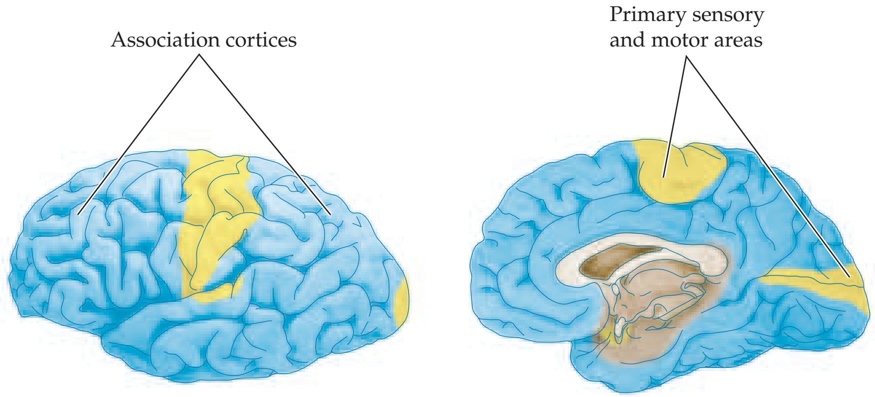


Figure 25.1 Lateral and medial views of the human brain, showing the extent of the association cortices in blue. The primary sensory and motor regions of the neocortex are shaded in yellow. Notice that the primary cortices occupy a relatively small fraction of the total area of the cortical mantle. The remainder of the neocortex—defined by exclusion as the association cortices—is the seat of human cognitive ability. The term *association* refers to the fact that these regions of the cortex integrate (associate) information derived from other brain regions.

tices in the parietal, temporal, and frontal lobes that make cognition possible. (The extrastriate cortex of the occipital lobe is equally important in cognition; its functions, however, are largely concerned with vision, and much of what is known about these areas has been discussed in Chapter 11.) These other areas of the cerebral cortex are referred to collectively as the **association cortices** (see Figure 25.1).

An Overview of Cortical Structure

Before delving into a more detailed account of the functions of these cortical regions, it is important to have a general understanding of cortical structure and the organization of its canonical circuitry. Most of the cortex that covers the cerebral hemispheres is **neocortex**, defined as cortex that has six cellular layers, or laminae. Each layer comprises more or less distinctive populations of cells based on their different densities, sizes, shapes, inputs, and outputs. The laminar organization and basic connectivity of the human cerebral cortex are summarized in Figure 25.2A and Table 25.1. Despite an overall uniformity, regional differences based on these laminar features have long been apparent (Box A), allowing investigators to identify numerous subdivisions of the cerebral cortex (Figure 25.2B). These histologically defined subdivisions are referred to as **cytoarchitectonic areas**, and, over the years, a zealous band of neuroanatomists has painstakingly mapped these areas in humans and in some of the more widely used laboratory animals.

Early in the twentieth century, cytoarchitectonically distinct regions were identified with little or no knowledge of their functional significance. Eventually, however, studies of patients in whom one or more of these cortical

TABLE 25.1
The Major Connections of the Neocortex

Sources of cortical input	*Targets of cortical output*
Other cortical regions	Other cortical regions
Hippocampal formation	Hippocampal formation
Amygdala	Amygdala
Thalamus	Thalamus
Brainstem modulatory systems	Caudate and putamen (striatum)
	Brainstem
	Spinal cord

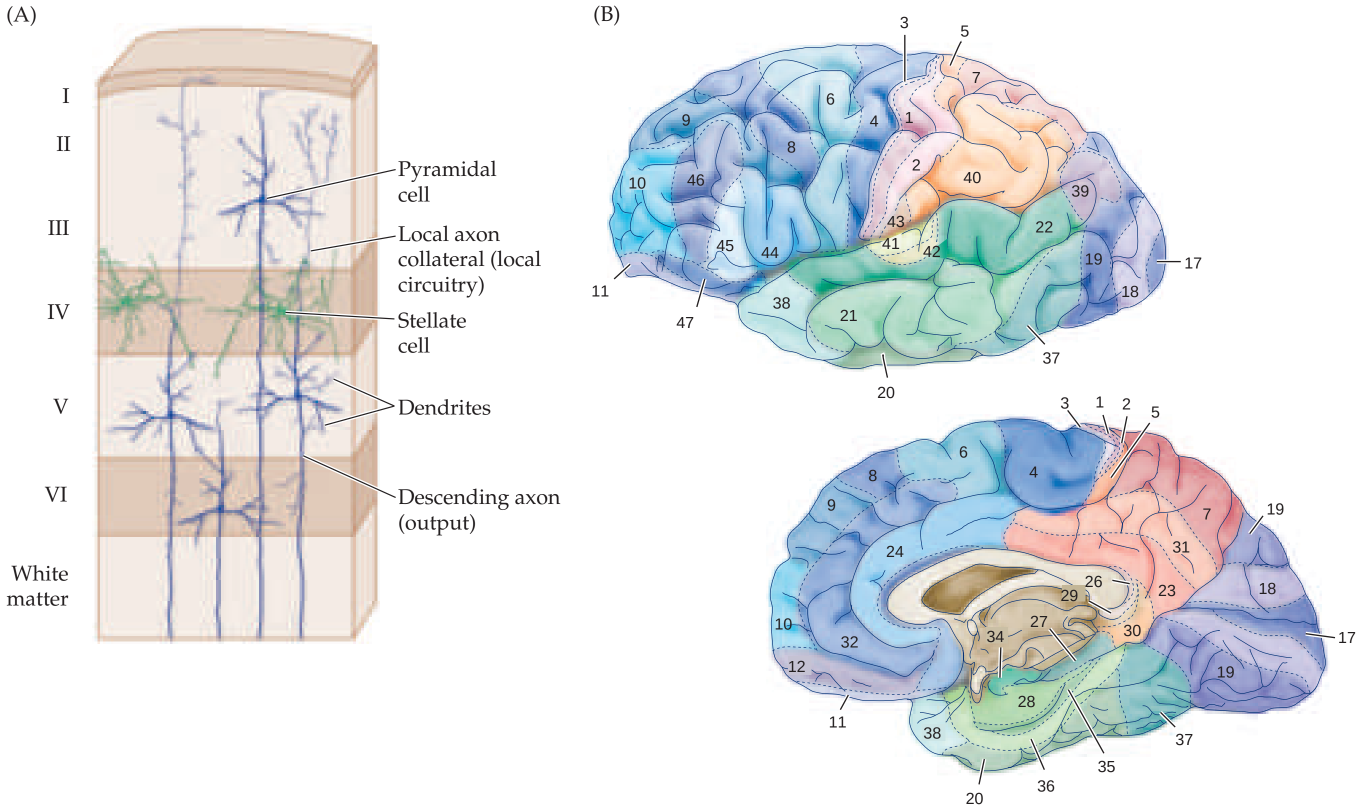


Figure 25.2 The structure of the human neocortex, including the association cortices. (A) A summary of the cellular composition of the six layers of the neocortex. (B) Based on variations in the thickness, cell density, and other histological features of the six neocortical laminae, the human brain can be divided into numerous cytoarchitectonic areas, in this case those recognized by the neuroanatomist Korbinian Brodmann in his seminal monograph in 1909. (See Box A for additional details.)

sylvius

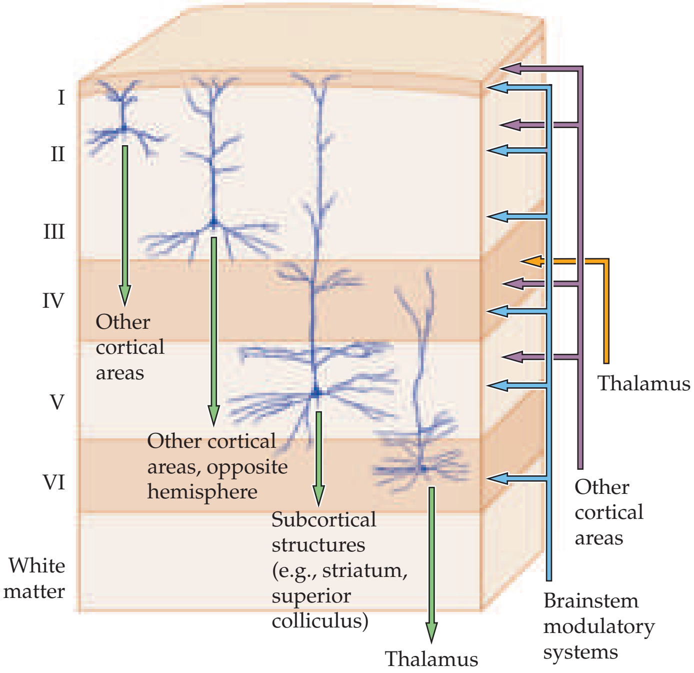
areas had been damaged, supplemented by electrophysiological mapping in both laboratory animals and neurosurgical patients, supplied this information. This work showed that many of the regions neuroanatomists had distinguished on histological grounds are also functionally distinct. Thus, cytoarchitectonic areas can sometimes be identified by the physiological response properties of their constituent cells, and often by their patterns of local and long-distance connections.

Despite significant variations among different cytoarchitectonic areas, the circuitry of all cortical regions has some common features (Figure 25.3). First, each cortical layer has a primary source of inputs and a primary output target. Second, each area has connections in the vertical axis (called *columnar* or *radial* connections) and connections in the horizontal axis (called *lateral* or *horizontal* connections). Third, cells with similar functions tend to be arrayed in radially aligned groups that span all of the cortical layers and receive inputs that are often segregated into radial or columnar bands. Finally, interneurons within specific cortical layers give rise to extensive local axons that extend horizontally in the cortex, often linking functionally similar groups of cells. The particular circuitry of any cortical region is a variation on this canonical pattern of inputs, outputs, and vertical and horizontal patterns of connectivity.

Specific Features of the Association Cortices

These generalizations notwithstanding, the connectivity of the association cortices is appreciably different from primary and secondary sensory and motor cortices, particularly with respect to inputs and outputs. For instance, two thalamic nuclei that are not involved in relaying primary motor or sensory information provide much of the subcortical input to the association

Figure 25.3 Canonical neocortical circuitry. Green arrows indicate outputs to the major targets of each of the neocortical layers in humans; orange arrow indicates thalamic input (primarily to layer IV); purple arrows indicate input from other cortical areas; and blue arrows indicate input from the brainstem modulatory systems to each layer.


I
II
III
IV
V
VI
White matter
Other cortical areas
Other cortical areas, opposite hemisphere
Subcortical structures (e.g., striatum, superior colliculus)
Thalamus
Thalamus
Other cortical areas
Brainstem modulatory systems

cortices: the **pulvinar** projects to the parietal association cortex, while the **medial dorsal nuclei** project to the frontal association cortex. Several other thalamic nuclei, including the anterior and ventral anterior nuclei, innervate the association cortices as well.

Unlike the thalamic nuclei that receive peripheral sensory information and project to primary sensory cortices, the input to these association cortex-projecting nuclei comes from other regions of the cortex. In consequence, the signals coming into the association cortices via the thalamus reflect sensory and motor information that has *already* been processed in the primary sensory and motor areas of the cerebral cortex, and is being fed back to the association regions. The primary sensory cortices, in contrast, receive thalamic information that is more directly related to peripheral sense organs (see, for example, Chapter 8). Similarly, much of the thalamic input to primary motor cortex is derived from the thalamic nuclei related to the basal ganglia and cerebellum rather than to other cortical regions (see Unit III).

A second major difference in the sources of innervation to the association cortices is their enrichment in *direct* projections from other cortical areas, called **corticocortical connections** (see Figure 25.3). Indeed, these connections form the majority of the input to the association cortices. Ipsilateral corticocortical connections arise from primary and secondary sensory and motor cortices, and from other association cortices within the same hemisphere. Corticocortical connections also arise from both corresponding and noncorresponding cortical regions in the opposite hemisphere via the corpus callosum and anterior commissure, which together are referred to as **interhemispheric connections**. In the association cortices of humans and other primates, corticocortical connections often form segregated bands or columns in which interhemispheric projection bands are interdigitated with bands of ipsilateral corticocortical projections.

Another important source of innervation to the association areas is subcortical, arising from the dopaminergic nuclei in the midbrain, the noradren-

Box A

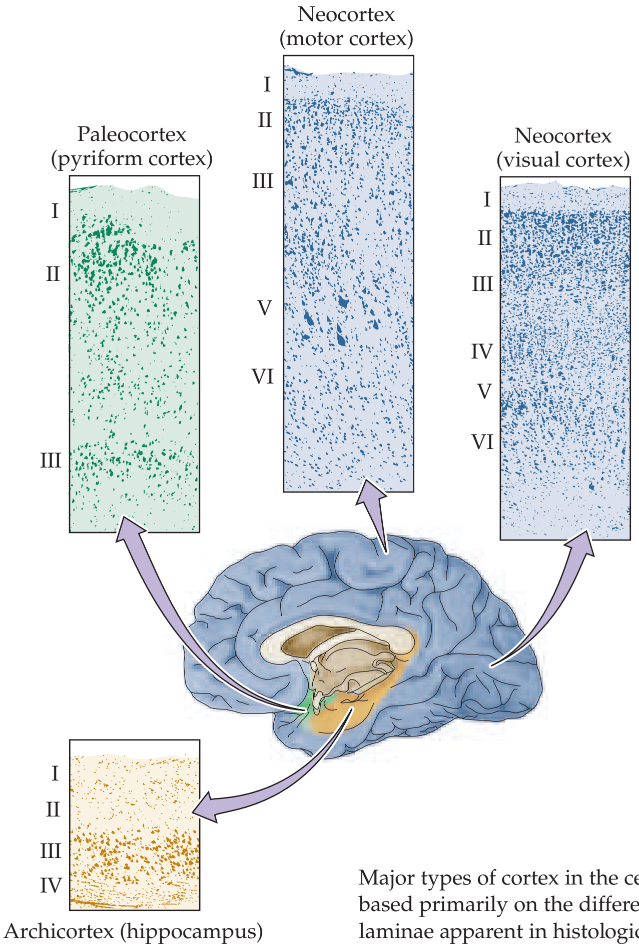
A More Detailed Look at Cortical Lamination

Much knowledge about the cerebral cortex is based on descriptions of differences in cell number and density throughout the cortical mantle. Nerve cell bodies, because of their high metabolic rate, are rich in basophilic substances (RNA, for instance), and therefore tend to stain darkly with reagents such as cresyl violet acetate. These *Nissl stains* (named after F. Nissl, who first described this technique when he was a medical student in nineteenth-century Germany) provide a dramatic picture of brain structure at the histological level. The most striking feature revealed in this way is the distinctive lamination of the cortex in humans and other mammals, as seen in the figure. In humans, there are three to six cortical layers, which are usually designated by roman numerals, with letters for laminar subdivisions (layers IVa, IVb, and IVc in the visual cortex, for example).

Each of the cortical laminae in the so-called *neocortex* (which covers the bulk of the cerebral hemispheres and is defined by six layers) has characteristic functional and anatomical features (see Figures 25.2 and 25.3). For example, cortical layer IV is typically rich in stellate neurons with locally ramifying axons; in the primary sensory cortices, these neurons receive input from the thalamus, the major sensory relay from the periphery. Layer V, and to a lesser degree layer VI, contain pyramidal neurons whose axons typically leave the cortex. The generally smaller pyramidal neurons in layers II and III (which are not as distinct as their roman numeral assignments suggest) have primarily corticocortical connections, and layer I contains mainly neuropil. Korbinian Brodmann, who early in the twentieth century devoted his career to an analysis of brain regions distinguished in this way, described about 50 distinct cortical regions, or cytoarchitectonic areas (see Figure 25.2B). These structural features of the cerebral cortex continue to figure importantly in discussions of the brain, particularly in structural/functional correlation of intensely studied regions such as the primary sensory and motor cortices.

Not all of the cortical mantle is six-layered neocortex. The hippocampus, for example, which lies deep in the temporal lobe and has been implicated in acquisition of declarative memories (see Chapter 30), has only three or four laminae. The hippocampal cortex is regarded as evolutionarily more primitive, and is therefore called *archicortex* to distinguish it from the six-layered neocortex. Another, presumably more primitive, type of cortex, called *paleocortex* (*paleo* = ancient), generally has three layers and is found on the ventral surface of the cerebral hemispheres and along the parahippocampal gyrus in the medial temporal lobe.

The functional significance of different numbers of laminae in neocortex, archicortex, and paleocortex is not known, although it seems likely that the greater number of layers in neocortex reflects more complex information processing than in archi- or paleocortex. The general similarity of neocortical structure across the entire cerebrum clearly suggests that there is a common denominator of cortical operation, although no one has yet deciphered what it is.



Major types of cortex in the cerebral mantle, based primarily on the different numbers of laminae apparent in histological sections.

ergic and serotonergic nuclei in the brainstem reticular formation, and cholinergic nuclei in the brainstem and basal forebrain. These diffuse inputs project to different cortical layers and, among other functions, determine mental state along a continuum that ranges from deep sleep to high alert (see Chapter 27).

The general wiring plan for the association cortices is summarized in Figure 25.4. Despite this degree of interconnectivity, the extensive inputs and outputs of the association cortices should not be taken to imply that everything is simply connected to everything else in these regions. On the contrary, each association cortex is defined by a distinct, if overlapping, subset of thalamic, corticocortical, and subcortical connections. It is nonetheless difficult to conclude much about the role of these different cortical areas based solely on connectivity (this information is, in any event, quite limited for the human association cortices; most of the evidence comes from anatomical tracing studies in non-human primates, supplemented by the limited pathway tracing that can be done in human brain tissue postmortem). As a result, inferences about the function of human association areas continue to depend critically on observations of patients with cortical lesions. Damage to the association cortices in the parietal, temporal, and frontal lobes, respectively, results in specific cognitive deficits that indicate much about the operations and purposes of each of these regions. These deductions have largely been corroborated by patterns of neural activity observed in the homologous regions of the brains of experimental animals, as well as in humans using noninvasive imaging techniques.

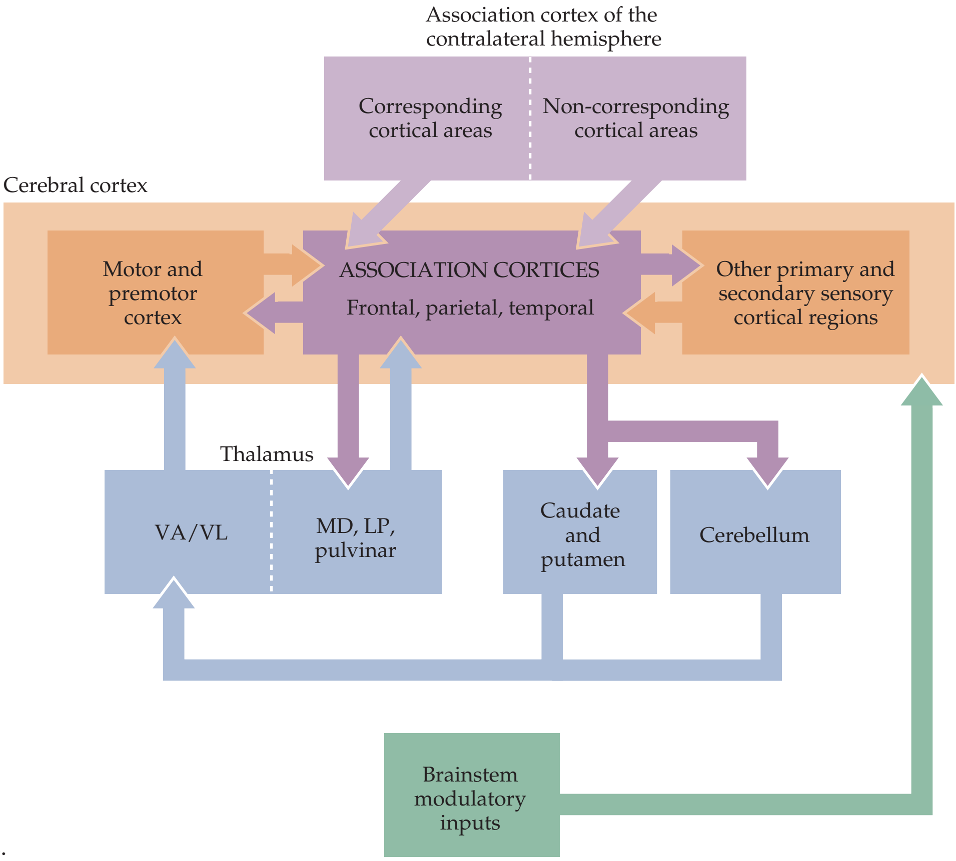

Association cortex of the contralateral hemisphere
Corresponding cortical areas
Non-corresponding cortical areas
Cerebral cortex
Motor and premotor cortex
ASSOCIATION CORTICES
Frontal, parietal, temporal
Other primary and secondary sensory cortical regions
Thalamus
VA/VL
MD, LP, pulvinar
Caudate and putamen
Cerebellum
Brainstem modulatory inputs

Figure 25.4 Summary of the overall connectivity of the association cortices.

Lesions of the Parietal Association Cortex: Deficits of Attention

In 1941, the British neurologist W. R. Brain reported three patients with unilateral parietal lobe lesions in whom the primary problem was varying degrees of attentional difficulty. Brain described their peculiar deficiency in the following way:

> Though not suffering from a loss of topographical memory or an inability to describe familiar routes, they nevertheless got lost in going from one room to another in their own homes, always making the same error of choosing a right turning instead of a left, or a door on the right instead of one on the left. In each case there was a massive lesion in the right parieto-occipital region, and it is suggested that this … resulted in an inattention to or neglect of the left half of external space.
>
> The patient who is thus cut off from the sensations which are necessary for the construction of a body scheme may react to the situation in several different ways. He may remember that the limbs on his left side are still there, or he may periodically forget them until reminded of their presence. He may have an illusion of their absence, i.e. they may 'feel absent' although he knows that they are there; he may believe that they are absent but allow himself to be convinced by evidence to the contrary; or, finally, his belief in their absence may be unamenable to reason and evidence to the contrary and so constitute a delusion.
>
> W. R. Brain, 1941 (*Brain* 64: pp. 257 and 264)

This description is generally considered the first account of the link between parietal lobe lesions and deficits in attention or perceptual awareness. Based on a large number of patients studied since Brain's pioneering work, these deficits are now referred to as **contralateral neglect syndrome**.

The hallmark of contralateral neglect is an inability to attend to objects, or even one's own body, in a portion of space, despite the fact that visual acuity, somatic sensation, and motor ability remain intact. Affected individuals fail to report, respond to, or even orient to stimuli presented to the side of the body (or visual space) opposite the lesion (Figure 25.5). They may also have difficulty performing complex motor tasks on the neglected side, including

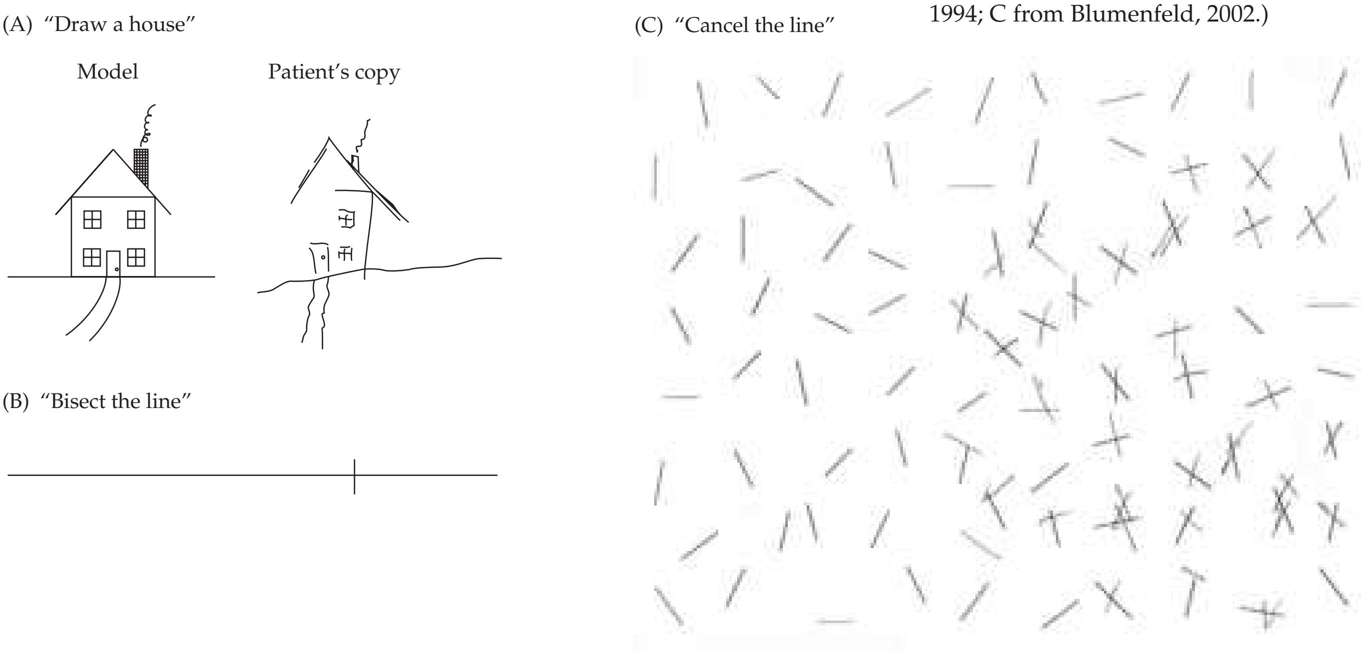


Figure 25.5 Characteristic performance on visuospatial tasks by individuals suffering from contralateral neglect syndrome. In (A), the patient was asked to draw a house by copying the figure on the left; on the right is the subject's imitation. In (B), the patient was asked to draw a vertical line through the center of (i.e., bisect) a horizontal line. In (C), the patient was asked to cross out each of the lines presented on the page (A, B adapted from Posner and Raichle, 1994; C from Blumenfeld, 2002.)

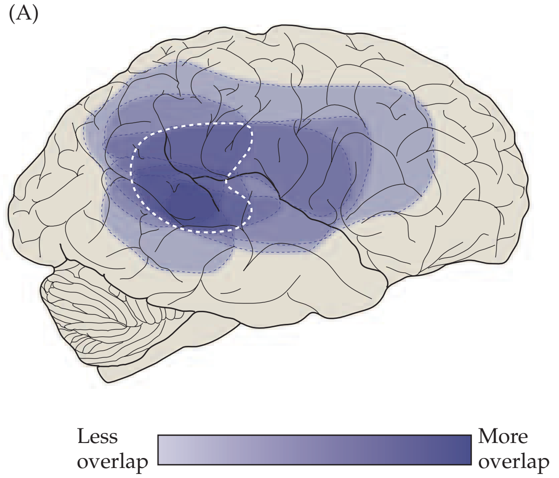
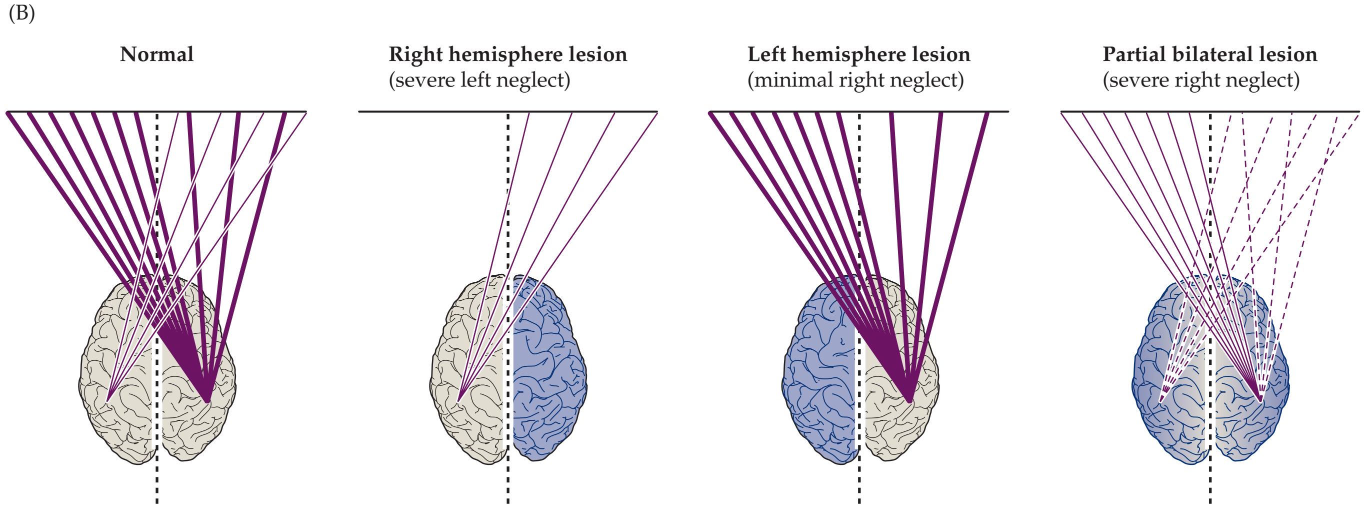


Figure 25.6 Neuroanatomy of attention. (A) Composite of the location of the underlying lesions in eight patients diagnosed with contralateral neglect syndrome. The site of damage was ascertained from CT scans (see Box B in Chapter 1). While the lesions include parietal cortical areas, frontal areas, and the temporal lobe of the right hemisphere, the region of the right parietal lobe indicated by the dashed line is most often affected. (B) Schematic illustration of hemispheric asymmetry in attention inferred from neglect patients. In normal subjects, the right parietal cortex dominates the control of attention, as indicated by the thicker rays. A right parietal lesion (purple) results in severe left neglect, whereas a left parietal lesion leads to only minimal right neglect due to preserved attention within the right hemisphere. Bilateral parietal lesions cause right neglect due to a lack of attentive processing in both hemispheres. (A after Heilman and Valenstein, 1985; B after Blumenfeld, 2002.)



dressing themselves, reaching for objects, writing, drawing, and, to a lesser extent, orienting to sounds (the motor deficits are called *apraxias*). The signs of neglect can be as subtle as a temporary lack of contralateral attention that rapidly improves as the patient recovers, or as profound as permanent denial of the existence of the side of the body and extrapersonal space opposite the lesion. Since Brain's original description of contralateral neglect and its relationship to lesions of the parietal lobe, it has been generally accepted that the parietal cortex, particularly the inferior parietal lobe, is the primary cortical region (but not the only region) governing attention (Figure 25.6A).

Importantly, contralateral neglect syndrome is specifically associated with damage to the *right* parietal cortex. The unequal distribution of this particular cognitive function between the hemispheres is thought to arise because the right parietal cortex mediates attention to both left and right halves of the body and extrapersonal space, whereas the left hemisphere mediates attention primarily to the right (Figure 25.6B). Thus, left parietal lesions tend to be compensated by the intact right hemisphere. In contrast, when the right parietal cortex is damaged, there is little or no compensatory capacity in the left hemisphere to mediate attention to the left side of the body or extrapersonal space.

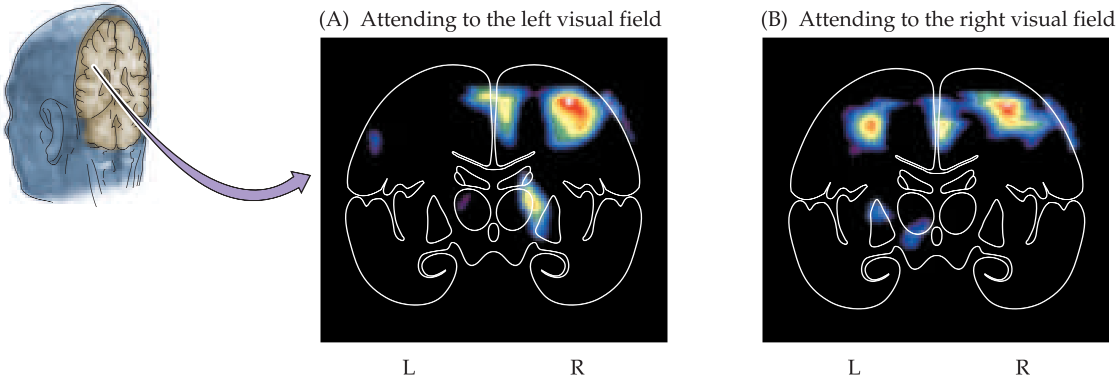

(A) Attending to the left visual field
(B) Attending to the right visual field
L
R
L
R

Figure 25.7 In confirmation of the impressions derived from neurological patients with parietal lobe damage, the right parietal cortex of normal subjects is highly active during tasks requiring attention. (A) A subject has been asked to attend to objects in the left visual field; only the right parietal cortex is active. (B) When attention is shifted from the left visual field to the right, the right parietal cortex remains active, but activity is apparent in the left parietal cortex as well. This arrangement implies that damage to the left parietal lobe does not generate right-sided hemineglect because the right parietal lobe also serves this function. (After Posner and Raichle, 1994.)

This interpretation has been confirmed by noninvasive imaging of parietal lobe activity during specific attention tasks carried out by normal subjects. Such studies show that blood flow is increased in *both* the right and left parietal cortices when subjects are asked to perform tasks in the *right* visual field requiring selective attention to distinct aspects of a visual stimulus such as its shape, velocity, or color. However, when a similar challenge is presented in the *left* visual field, only the *right* parietal cortex is activated (Figure 25.7). There is also evidence of increased activity in the right frontal cortex during such tasks (see Figure 25.6A). This latter observation suggests that regions outside the parietal lobe also contribute to attentive behavior, and perhaps to some aspects of the pathology of neglect syndromes. Overall, however, metabolic mapping is consistent with the clinical fact that contralateral neglect typically arises from a right parietal lesion, and endorses the broader idea of hemispheric specialization for attention, in keeping with hemispheric specialization for a number of other cognitive functions (see below and Chapter 26).

Interestingly, patients with contralateral neglect are not simply deficient in their attentiveness to the left visual field, but to the left sides of objects generally. For example, when asked to cross out lines distributed throughout the visual field, contralateral neglect patients, as expected, tend to bisect more lines on the right side of the field than on the left, consistent with a disruption in attentiveness to the left visual field (see Figure 25.5C). The lines they draw, however, tend to be biased towards the right side of each nonvertical line, wherever the line happens to be in the visual field. These observations suggest that attentiveness relies on a frame of reference anchored to the locations of objects and their relative dimensions.

Disruptions in spatial frames of reference are also associated with lesions of the parietal cortex that are more dorsal and medial than those typically associated with classical neglect. Such damage often presents as a triad of visuospatial deficits known as Balint's syndrome (named after an Austrian-Hungarian neurologist). These three signs are: an inability to perceive parts of a complex visual scene as a whole (called *simultanagnosia*); deficits in visually guided reaching (*optic ataxia*); and difficulty in voluntary scanning of visual scenes (*ocular apraxia*). In contrast to classical neglect, optic ataxia and ocular apraxia typically remit when movements are guided by non-visual cues. These observations suggest that the parietal cortex participates in the construction of spatial representations that can guide both attention and movement.

Lesions of the Temporal Association Cortex: Deficits of Recognition

Clinical evidence from patients with lesions of the association cortex in the temporal lobe indicates that one of the major functions of this part of the brain is the recognition and identification of stimuli that are attended to, particularly complex stimuli. Thus, damage to either temporal lobe can result in difficulty recognizing, identifying, and naming different categories of objects. These disorders, collectively called **agnosias** (from the Greek for "not knowing"), are quite different from the neglect syndromes. As noted, patients with right parietal lobe damage often deny awareness of sensory information in the left visual field (and are less attentive to the left sides of objects generally), despite the fact that the sensory systems are intact (an individual with contralateral neglect syndrome typically withdraws his left arm in response to a pinprick, even though he may not admit the arm's existence). Patients with agnosia, on the other hand, acknowledge the presence of a stimulus, but are unable to report what it is. These latter disorders have both a lexical aspect (a mismatching of verbal or other cognitive symbols with sensory stimuli; see Chapter 26) and a mnemonic aspect (a failure to recall stimuli when confronted with them again; see Chapter 30).

One of the most thoroughly studied agnosias following damage to the temporal association cortex in humans is the inability to recognize and identify faces. This disorder, called **prosopagnosia** (*prosopo*, from the Greek for "face" or "person"), was recognized by neurologists in the late nineteenth century and remains an area of intense investigation. After damage to the inferior temporal cortex, typically on the right, patients are often unable to identify familiar individuals by their facial characteristics, and in some cases cannot recognize a face at all. Nonetheless, such individuals are perfectly aware that some sort of visual stimulus is present and can describe particular aspects or elements of it without difficulty.

An example is the case of L.H., a patient described by the neuropsychologist N. L. Etcoff and colleagues. (The use of initials to identify neurological patients in published reports is standard practice.) This 40-year-old minister and social worker had sustained a severe head injury as the result of an automobile accident when he was 18. After recovery, L.H. could not recognize familiar faces, report that they were familiar, or answer questions about faces from memory. He was nonetheless able to lead a fairly normal and productive life. He could still identify other common objects, could discriminate subtle shape differences, and could recognize the sex, age, and even the "likability" of faces. Moreover, he could identify particular people by non-facial cues such as voice, body shape, and gait. The only other category of visual stimuli he had trouble recognizing was animals and their expressions, though these impairments were not as severe as for human faces. Noninvasive brain imaging showed that L.H.'s prosopagnosia was the result of damage to the right temporal lobe.

More recently, imaging studies in normal subjects have confirmed that the inferior temporal cortex mediates face recognition and that nearby regions are responsible for categorically different recognition functions (Figure 25.8). In general, lesions of the right temporal cortex lead to agnosia for faces and objects, whereas lesions of the corresponding regions of the left temporal cortex tend to result in difficulties with language-related material. (Recall that the primary auditory cortex is on the superior aspect of the temporal lobe; as described in the following chapter, the cortex adjacent to the auditory cortex in the left temporal lobe is specifically concerned with language.)

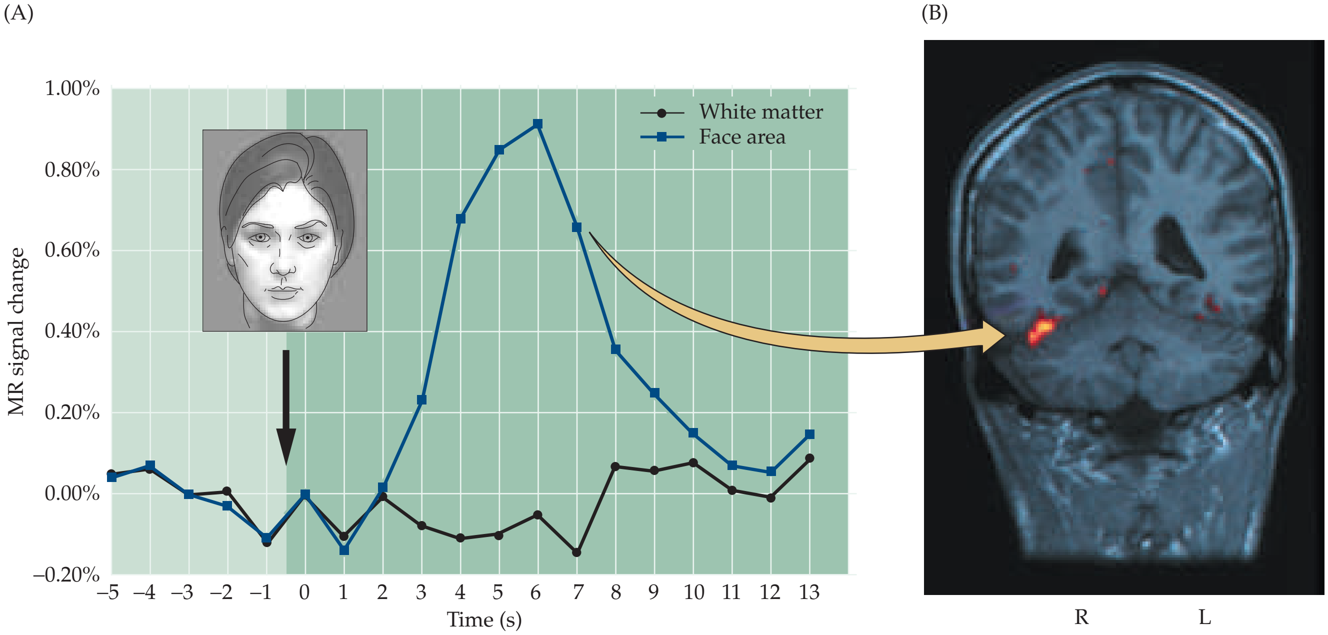


Figure 25.8 Functional brain imaging of temporal lobe during face recognition. (A) Face stimulus presented to a normal subject at time indicated by arrow. Graph shows activity change in the relevant area of the right temporal lobe. (B) Location of fMRI activity in the right inferior temporal lobe. (Courtesy of Greg McCarthy.)

The lesions that typically cause recognition deficits are in the inferior temporal cortex in or near the so-called fusiform gyrus; those that cause language-related problems in the left temporal lobe tend to be on the lateral surface of the cortex. Consistent with these conclusions, direct cortical stimulation in subjects whose temporal lobes are being mapped for neurosurgery (typically removal of an epileptic focus) may have a transient prosopagnosia as a consequence of this abnormal activation of the relevant regions of the right temporal cortex.

Prosopagnosia and related agnosias involving objects are specific instances of a broad range of functional deficits that have as their hallmark the inability to recognize a complex sensory stimulus as familiar, and to identify and name that stimulus as a meaningful entity in the environment. Depending on the laterality, location, and size of the lesion in temporal cortex, agnosias can be as specific as for human faces, or as general as an inability to name most familiar objects.

Lesions of the Frontal Association Cortex: Deficits of Planning

The functional deficits that result from damage to the human frontal lobe are diverse and devastating, particularly if both hemispheres are involved. This broad range of clinical effects stems from the fact that the frontal cortex has a wider repertoire of functions than any other neocortical region (consistent with the fact that the frontal lobe in humans and other primates is the largest of the brain's lobes and comprises a greater number of cytoarchitectonic areas).

The particularly devastating nature of the behavioral deficits after frontal lobe damage reflects the role of this part of the brain in maintaining what is normally thought of as an individual's "personality." The frontal cortex integrates complex perceptual information from sensory and motor cortices, as well as from the parietal and temporal association cortices. The result is an appreciation of self in relation to the world that allows behaviors to be planned and executed normally. When this ability is compromised, the afflicted individual often has difficulty carrying out complex behaviors that are appropriate to the circumstances. These deficiencies in the normal ability to match ongoing behavior to present or future demands are, not surprisingly, interpreted as a change in the patient's "character."

The case that first called attention to the consequences of frontal lobe damage was that of Phineas Gage, a worker on the Rutland and Burlington Railroad in mid-nineteenth-century Vermont. In that era, the conventional way of blasting rock was to tamp powder into a hole with a heavy metal rod. Gage, the popular and respected foreman of the crew, was undertaking this procedure one day in 1848 when his tamping rod sparked the powder, setting off an explosion that drove the rod, which was about a meter long and 4 or 5 centimeters in diameter, through his left orbit (eye socket), destroying much of the frontal part of his brain in the process (see the illustration on page 612). Gage, who never lost consciousness, was promptly taken to a local doctor who treated his wound. An infection set in, presumably destroying additional frontal lobe tissue, and Gage was an invalid for several months. Eventually he recovered and was to outward appearances well again. Those who knew Gage, however, were profoundly aware that he was not the "same" individual that he had been before. A temperate, hard-working, and altogether decent person had, by virtue of this accident, been turned into an inconsiderate, intemperate lout who could no longer cope with normal social intercourse or the kind of practical planning that had allowed Gage the social and economic success he enjoyed before.

The physician who looked after Gage until his death in 1863 summarized his impressions of Gage's personality as follows:

> [Gage is] fitful, irreverent, indulging at times in the grossest profanity (which was not previously his custom), manifesting but little deference for his fellows, impatient of restraint or advice when it conflicts with his desires, at times pertinaciously obstinate, yet capricious and vacillating, devising many plans of future operations, which are no sooner arranged than they are abandoned in turn for others appearing more feasible. A child in his intellectual capacity and manifestations, he has the animal passions of a strong man. Previous to his injury, although untrained in the schools, he possessed a well-balanced mind, and was looked upon by those who knew him as a shrewd, smart businessman, very energetic and persistent in executing all his plans of operation. In this regard his mind was radically changed, so decidedly that his friends and acquaintances said he was 'no longer Gage.'
>
> J. M. Harlow, 1868 (*Publications of the Massachusetts Medical Society* 2: 339–340)

Another classic case of frontal lobe deficits was that of a patient followed for many years by the neurologist R. M. Brickner during the 1920s and 30s. Joe A., as Brickner referred to his patient, was a stockbroker who at age 39 underwent bilateral frontal lobe resection because of a large tumor. After the operation, Joe A. had no obvious sensory or motor deficits; he could speak and understand verbal communication and was aware of people, objects, and temporal order in his environment. He acknowledged his illness and retained a high degree of intellectual power, as judged from an ongoing ability to play an expert game of checkers. Nonetheless, Joe A.'s personality had undergone a dramatic change. This formerly restrained, modest man became boastful of professional, physical, and sexual prowess, showed little

Box B

Psychosurgery

The consequences of frontal lobe destruction have been all too well documented by a disturbing yet fascinating episode in twentieth-century medical practice. During the period from 1935 through the 1940s, neurosurgical destruction of the frontal lobe (frontal lobotomy or leukotomy) was a popular treatment for certain mental disorders. More than 20,000 of these procedures were performed, mostly in the United States.

Enthusiasm for this approach to mental disease grew from the work of Egas Moniz, a respected Portuguese neurologist, who, among other accomplishments, did pioneering work on cerebral angiography before becoming the leading advocate of psychosurgery. Moniz recognized that the frontal lobes were important in personality structure and behavior, and concluded that interfering with frontal lobe function might alter the course of mental diseases such as schizophrenia and other chronic psychiatric disorders. He also recognized that destroying the frontal lobe would be relatively easy to do and, with the help of Almeida Lima, a neurosurgical colleague, introduced a simple surgical procedure for indiscriminately destroying most of the connections between the frontal lobe and the rest of the brain (see figure).

In the United States, the neurologist Walter Freeman at George Washington University School of Medicine, in collaboration with neurosurgeon James Watts, became an equally strong advocate of this approach. Freeman devoted his life to treating a wide variety of mentally disturbed patients in this way. He popularized a form of the procedure that could be carried out under local anesthesia and traveled widely across the United States to demonstrate this technique and encourage its use.

Although it is easy in retrospect to be critical of this zealotry in the absence of either evidence or sound theory, it is important to remember that effective psychotropic drugs were not then available, and patients suffering from many of the disorders for which leukotomies were done were confined under custodial conditions that were at best dismal, and at worst brutal. Rendering a patient relatively tractable, albeit permanently altered in personality, no doubt seemed the most humane of the difficult choices that faced psychiatrists and others dealing with such patients in that period.

With the advent of increasingly effective psychotropic drugs in the late 1940s and the early 1950s, frontal lobotomy as a psychotherapeutic strategy rapidly disappeared, but not before Moniz was awarded the Nobel Prize for Physiology or Medicine in 1949. The history of this instructive episode in modern medicine has been compellingly told by Eliot Valenstein, and his book on the rise and fall of psychosurgery should be read by anyone contemplating a career in neurology, neurosurgery, or psychiatry.

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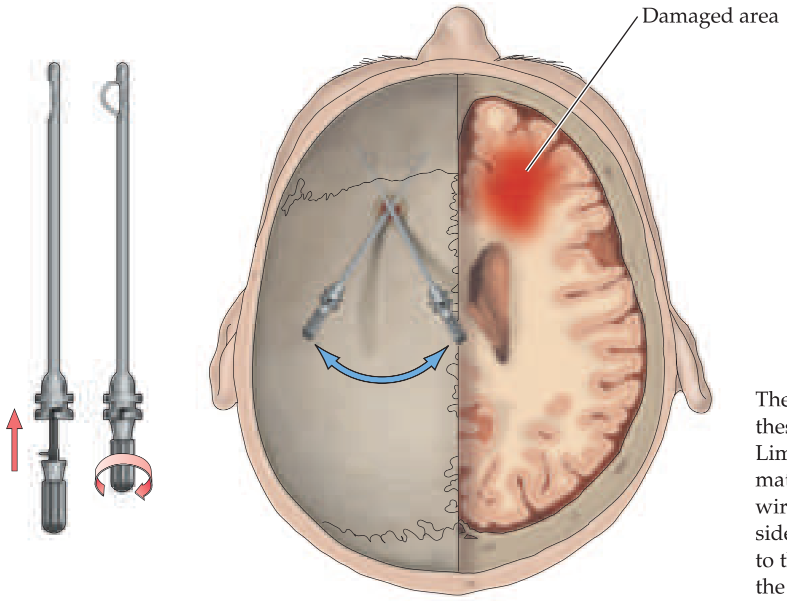


The surgical technique for frontal leukotomy under local anesthesia described and advocated by Egas Moniz and Almeida Lima. The "leukotome" was inserted into the brain at approximately the angles shown. When the leukotome was in place, a wire "knife" was extended and the handle rotated. The right side of the figure depicts a horizontal slice of the brain (parallel to the top of the skull) with Moniz's estimate of the extent of the damage done by the procedure. (After Moniz, 1937.)

restraint in conversation, and was unable to match the appropriateness of what he said to his audience. Like Gage, his ability to plan for the future was largely lost, as was much of his earlier initiative and creativity. Even though he retained the ability to learn complex procedures, he was unable to return to work and had to rely on his family for support and care.

The effects of widespread frontal lobe damage documented by these case studies encompass a wide range of cognitive disabilities, including impaired restraint, disordered thought, perseveration (i.e., repetition of the same behavior), and the inability to plan appropriate action. Recent studies of patients with focal damage to particular regions of the frontal lobe also suggest that some of the processes underlying these deficits may be localized anatomically, with working memory functions (see Chapter 30) situated more dorsolaterally and planning and social restraint functions located more ventromedially. Some of these functions can be clinically assessed using standardized tests such as the Wisconsin Card Sorting Task for planning (see Box C), the delayed response task for working memory, and the "go-nogo" task for inhibition of inappropriate responses. All these observations are consistent with the idea that the common denominator of the cognitive functions subserved by the frontal cortex is the selection, planning, and execution of appropriate behavior, particularly in social contexts.

Sadly, the effects of damage to the frontal lobes have also been documented by the many thousands of frontal lobotomies ("leukotomies") performed in the 1930s and 40s as a means of treating mental illness (Box B). The rise and fall of this "psychosurgery" provides a compelling example of the frailty of human judgment in medical practice, and of the conflicting approaches of neurologists, neurosurgeons, and psychiatrists in that era to the treatment of mental disease.

"Attention Neurons" in the Monkey Parietal Cortex

These clinical and pathological observations clearly indicate distinct cognitive functions for the parietal, temporal, and frontal lobes. They do not, however, provide much insight into how the nervous system represents this information in nerve cells and their interconnections. The apparent functions of the association cortices implied by clinical observations stimulated a number of informative electrophysiological studies in non-human primates, particularly macaque (usually rhesus) monkeys.

As in humans, a wide range of cognitive abilities in monkeys are mediated by the association cortices of the parietal, temporal, and frontal lobes (Figure 25.9A). Moreover, these functions can be tested using behavioral paradigms that assess attention, identification, and planning capabilities—the broad functions respectively assigned to the parietal, temporal, and frontal association cortices in humans. Needless to say, it is far more practical to study neuronal activity in relation to cognitive functions in experimental animals. Using implanted electrodes, recordings can be made from single neurons in the brains of awake, behaving monkeys to assess the activity of individual cells in the association cortices as various cognitive tasks are performed (Figure 25.9B).

An example is neurons apparently related to the attentive functions of the parietal cortex. These particular studies of cellular electrophysiology and behavior take advantage of the fact that monkeys can be trained to selectively attend to particular objects or events and report their experience in a variety of nonverbal ways, typically by looking at a response target or manipulating a joystick. Thus, attention-sensitive neurons can be identified

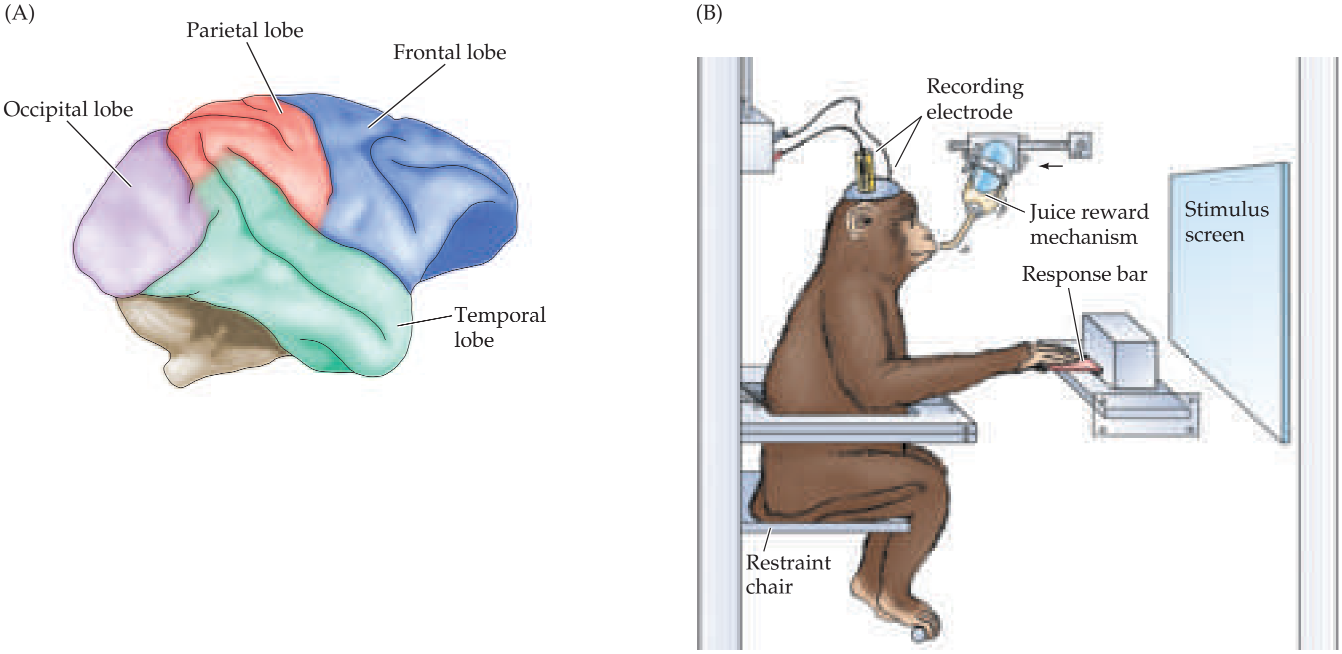


Figure 25.9 Recording from single neurons in the brain of an awake, behaving rhesus monkey. (A) Lateral view of the rhesus monkey brain showing the parietal (red), temporal (green), and frontal (blue) cortices. The occipital cortex is shaded purple. (B) The animal is seated in a chair and gently restrained. Several weeks before data collection begins, a recording well is placed through the skull using a sterile surgical technique. For electrophysiological recording experiments, a tungsten microelectrode is inserted through the dura and arachnoid, and into the cortex. The screen and the response bar in front of the monkey are for behavioral testing. In this way, individual neurons can be monitored while the monkey performs specific cognitive tasks.

by changes in neuronal activity associated with simultaneous changes in the attentive behavior of the animal. As might be expected from the clinical evidence in humans, neurons in specific regions of the parietal cortex of the rhesus monkey are activated when the animal attends to a target but not when the same stimulus is ignored (Figure 25.10B).

In another study, monkeys were rewarded with different amounts of fruit juice (a highly desirable treat) for attending to each of a pair of simultaneously illuminated targets (Figure 25.10C). Not surprisingly, the frequency with which monkeys attended to each target varied with the amount of juice they could expect for doing so. Moreover, the activity of some neurons in parietal cortex also varied systematically as a function of the amount of juice associated with each target, and therefore the amount of attention paid by the monkey to the target. Thus, the primate parietal cortex contains neurons that respond specifically when the animal attends to a behaviorally meaningful stimulus, and the vigor of the response reflects the amount of attention paid to the stimulus.

"Recognition Neurons" in the Monkey Temporal Cortex

In keeping with human deficits of recognition following temporal lobe lesions, neurons with responses that correlate with the recognition of specific

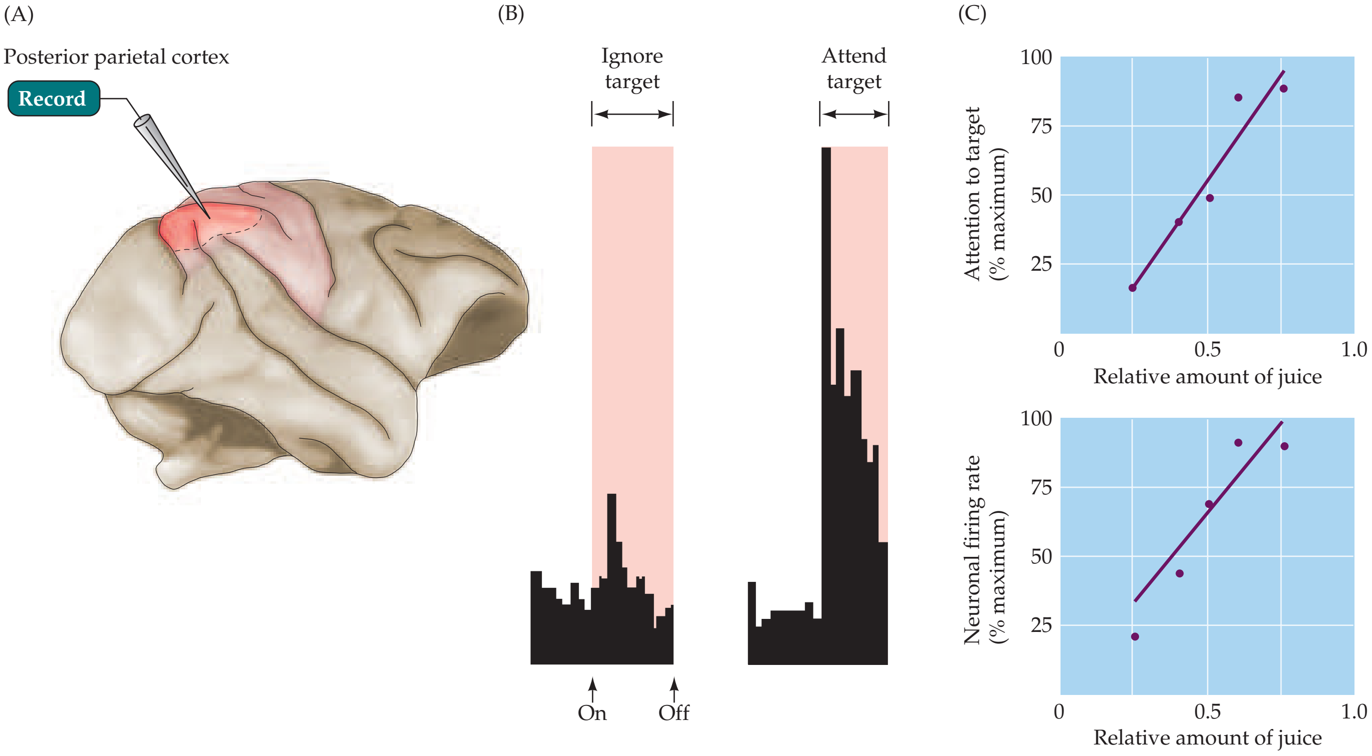


Figure 25.10 Selective activation of neurons in the parietal cortex of a rhesus monkey as a function of attention (in this case, attention is directed to a light associated with a fruit juice reward). (A) Region of recording. (B) Although the baseline level of activity of the neuron being studied here remains unchanged when the monkey ignores a visual target (left), firing rate increases dramatically when the monkey attends to the same stimulus (right). The histograms indicate action potential frequency per unit time. (C) When given a choice of where to attend, the monkey pays increasing attention to a particular visual target when more fruit juice reward can be expected for doing so (left), and the firing rate of a parietal neuron under study increases accordingly (B after Lynch et al., 1977. C after Platt and Glimcher, 1999.)

stimuli are present in the temporal cortex of rhesus monkeys (Figure 25.11). The behavior of these neurons in the vicinity of the superior temporal sulcus is generally consistent with one of the major functions ascribed to the human temporal cortex—namely, the recognition and identification of complex stimuli. For example, some neurons in the inferior temporal gyrus of the rhesus monkey cortex respond specifically to the presentation of a monkey face. These cells are often quite selective; thus, some respond only to the frontal view of a face and others only to profiles (Figure 25.11B,C). Furthermore, the cells are not easily deceived. When parts of faces or generally similar objects are presented, such cells typically fail to respond.

In principle, it is unlikely that such "face cells" are tuned to specific faces or objects, and no cells have so far been found that are selective for a particular face. However, it is not hard to imagine that populations of neurons differently responsive to various features of faces or other objects could act in concert to enable the recognition of such complex sensory stimuli. In fact, recent studies

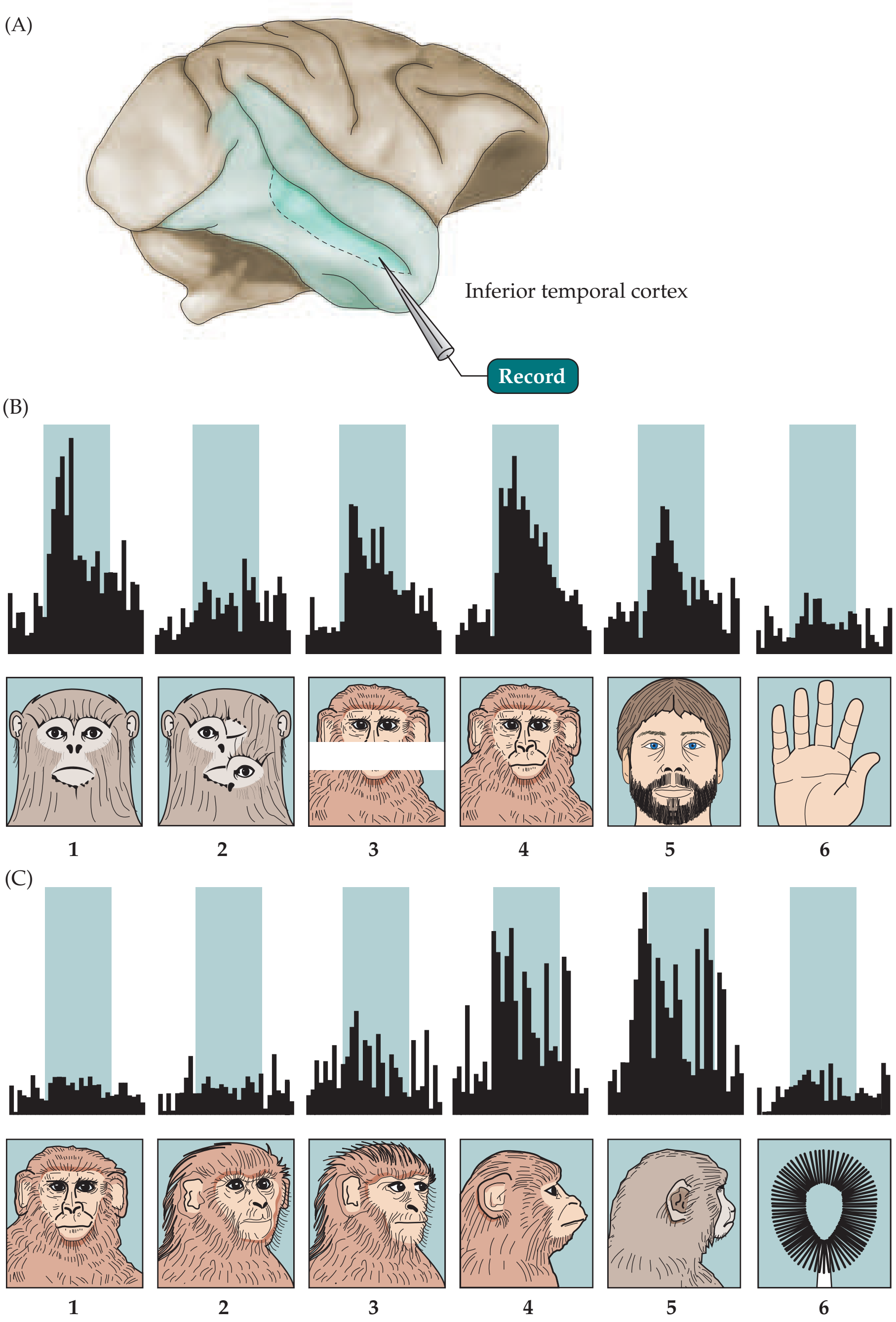


Figure 25.11 Selective activation of face cells in the inferior temporal cortex of a rhesus monkey. (A) Region of recording. (B) The neuron being recorded from in this case responds selectively to faces seen from the front. Scrambled parts of faces (stimulus 2) or faces with parts omitted (stimulus 3) do not elicit a maximal response. The cell responds best to different monkey faces, as long as they are complete and viewed from the front (stimulus 4); the cell also responds to a bearded human face (stimulus 5), although not quite as robustly. An irrelevant stimulus (a hand; stimulus 6) does not elicit a response. (C) In this example, the neuron being recorded from responds to profiles of faces. A face viewed from the front (stimulus 1), 30° (stimulus 2), or 60° (stimulus 3) is not as effective as a true profile (stimulus 4). The cell responds to profiles of different monkeys (stimulus 5), but is unresponsive to an irrelevant stimulus (a brush; stimulus 6). (After Desimone et al., 1984.)

have suggested that neurons in the temporal cortex may be organized in a columnar arrangement similar to that in the primary visual cortex (see Chapter 11). Each column is thought to represent different arrangements of complex features making up an object, while the center of neuronal activity within this map indicates the object in view. In keeping with this general idea, optical imaging (see Box C in Chapter 11) of the surface of the temporal cortex shows that large populations of neurons are activated when monkeys view an object comprising several different geometric features. The locus of this activity in the

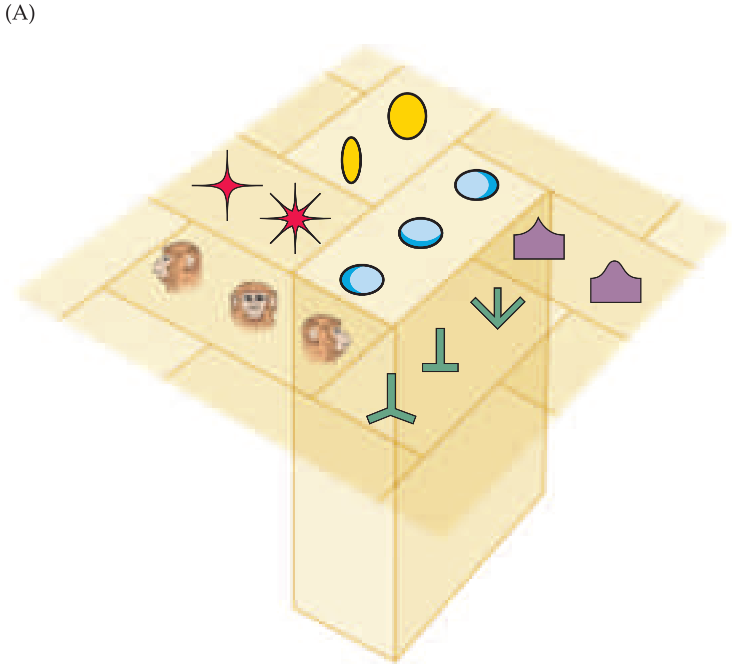
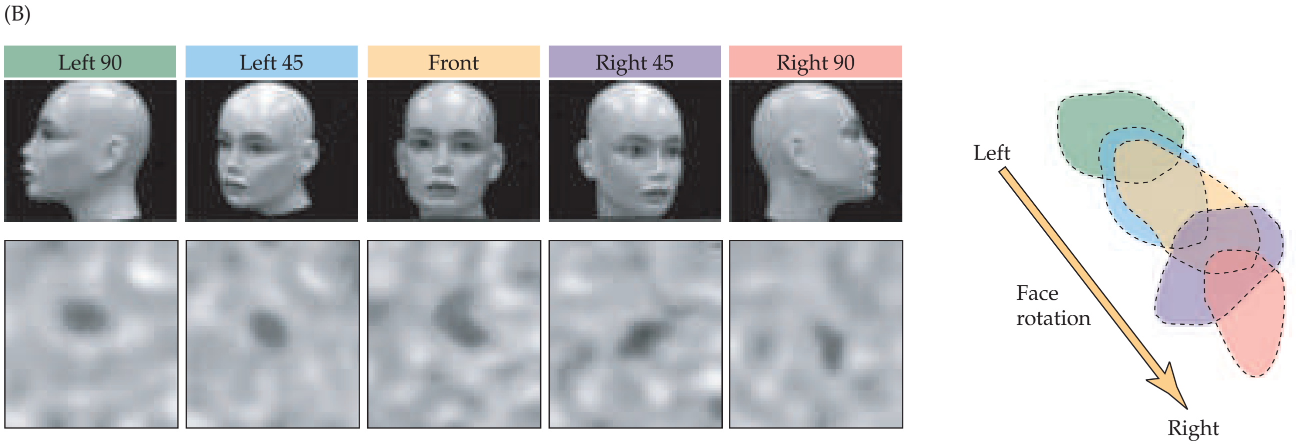


Figure 25.12 Topography of object representation. (A) Schematic of possible columnar organization of object representations in the inferotemporal cortex. Each cortical column is thought to signal a particular object class or point of view, with relatively smooth transitions between object features across columns. (B) Systematic movement of the active region of inferotemporal cortex with rotation of the face. Intrinsic signal optical images (below) were obtained for the views of five different positions of the face. Contours circumscribing significant cortical activation by these five different views are shown on the right. (A after Tanaka, 2001; B after Wang et al., 1996.)



upper layers of the cortex shifts systematically when object features, such as the orientation of a face, are systematically altered (Figure 25.12). These further observations suggest that object identification relies on graded signals carried by a population of neurons rather than on the specific output of one or a few cells selective for a particular object.

"Planning Neurons" in the Monkey Frontal Cortex

In confirmation of the human clinical evidence about the function of the frontal association cortices, neurons that appear to be specifically involved in planning have been identified in the frontal cortices of rhesus monkeys.

The behavioral test used to study cells in the monkey frontal cortex is called the **delayed response task** (Figure 25.13A). Variants of this task are used to assess frontal lobe function in a variety of situations, including the

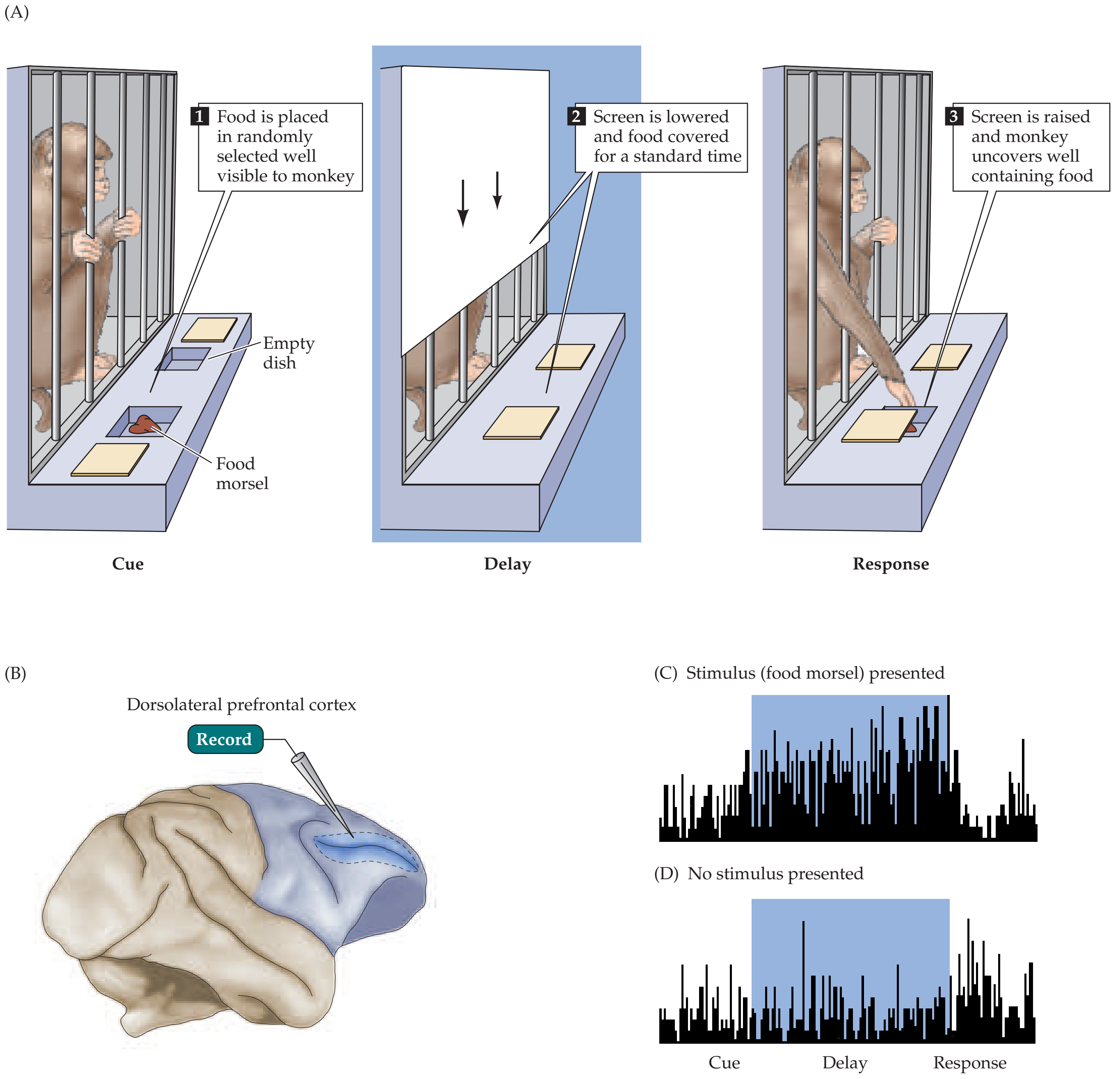
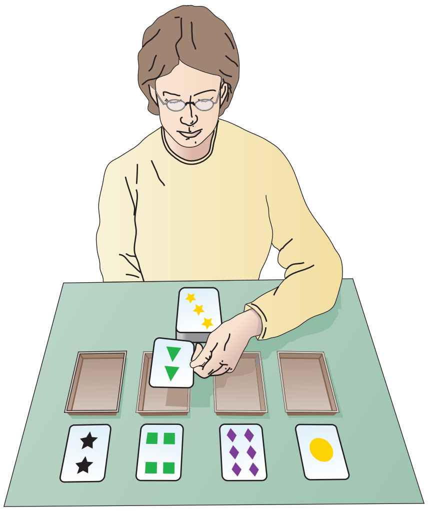

(A)
1 Food is placed in randomly selected well visible to monkey
Empty dish
Food morsel
2 Screen is lowered and food covered for a standard time
3 Screen is raised and monkey uncovers well containing food
Cue
Delay
Response
(B)
Dorsolateral prefrontal cortex
Record
(C) Stimulus (food morsel) presented
(D) No stimulus presented
Cue
Delay
Response

Figure 25.13 Activation of neurons near the principal sulcus of the frontal lobe during delayed response task. (A) Illustration of task. The experimenter randomly varies the well in which the food is placed. The monkey watches the morsel being covered, and then the screen is lowered for a standard time. When the screen is raised, the monkey is allowed to uncover only one well to retrieve the food. Normal monkeys learn this task quickly, usually performing at a level of 90% correct after less than 500 training trials, whereas monkeys with frontal lesions perform poorly. (B) Region of recording. (C) Activity of a delay-specific neuron in the prefrontal cortex of a rhesus monkey recorded during the delayed response task shown in (A). The histograms show the number of action potentials during the cue, delay, and response periods. The neuron begins firing when the screen is lowered and remains active throughout the delay period. (D) When the screen is lowered and raised but no food is presented, the same neuron is less active. (After Goldman-Rakic, 1987.)

Box C

Neuropsychological Testing

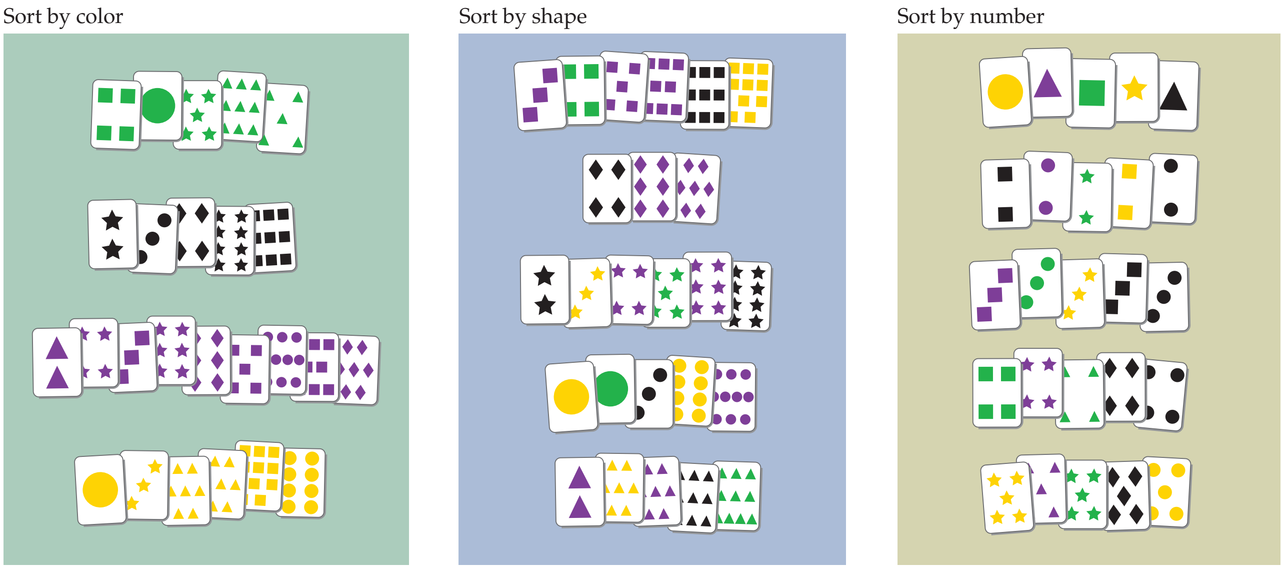
Long before PET scanning and functional MRI were used to evaluate normal and abnormal cognitive function, several "low-tech" methods proved to be reliable means of assessing these abilities in human subjects. From the late 1940s onward, psychologists and neurologists developed a battery of behavioral tests—generally called neuropsychological tests—to evaluate the integrity of cognitive function and to help localize lesions.



One of the most frequently used measures is the Wisconsin Card Sorting Task illustrated here. In this test, the examiner places four cards with symbols that differ in number, shape, or color before the subject, who is given a set of response cards with similar symbols on them. The subject is then asked to place an appropriate response card in front of the stimulus card based on a sorting rule established, but not stated, by the examiner (i.e., sort by color, number, or shape). The examiner then indicates whether the response is "right" or "wrong." After 10 consecutive correct responses, the examiner changes the sorting rule simply by saying "wrong." The subject must then ascertain the new sorting rule and perform 10 correct trials. The sorting rule is then changed again, until six cycles have been completed.

In 1963, the neuropsychologist Brenda Milner at the Montreal Neurological Institute showed that patients with frontal lobe lesions have consistently poor performance in the Wisconsin Card Sorting Task. By comparing patients with known brain lesions as a result of surgery for epilepsy or tumor, Milner was able to demonstrate that this impairment is fairly specific for frontal lobe damage. Particularly striking is the inability of frontal lobe patients to use previous information to guide subsequent behavior. A widely accepted explanation for the sensitivity of the Wisconsin Card Sorting Task to frontal lobe deficits is the "planning" aspect of this test. To respond correctly, the subject must retain information about the previous trial, which is then used to guide behavior on future trials. Processing this sort of information is characteristic of frontal lobe function.

A variety of other neuropsychological tests have been devised to evaluate the functional integrity of other cognitive functions. These include tasks in which a patient is asked to identify familiar faces in a series of pictures, and others in which "distractors" interfere with the patient's ability to attend to salient stimulus features. An example of the latter is the Stroop Interference Test, in which patients are asked to read the names of colors presented in color-conflicting print



Sort by color

Sort by shape

Sort by number

(for example, the word "green" printed in red ink). This sort of challenge evaluates both attention and identification abilities.

The simplicity, economy, and accumulated experience with such tests continue to make them a valuable means of evaluating cognitive functions.

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clinical evaluation of frontal lobe function in humans (Box C). In the delayed response task, the monkey watches an experimenter place a food morsel in one of two wells; both wells are then covered. Subsequently, a screen is lowered for an interval of a few seconds to several minutes (the delay). When the screen is raised, the monkey gets only one chance to uncover the well containing food and receive the reward. Thus, the animal must decide that he wants the food, remember where it is placed, recall that the cover must be removed to obtain the food, and keep all this information available during the delay so that it can be used to get the reward. The monkey's ability to carry out this task is diminished or abolished if the area anterior to the motor region of the frontal cortex—called the prefrontal cortex—is destroyed bilaterally (which is in accord with clinical findings in human patients).

Some neurons in the prefrontal cortex, particularly those in and around the principal sulcus (Figure 25.13B), are activated when monkeys perform the delayed response task, and they are maximally active during the period of the delay, as if their firing represented information about the location of the food morsel maintained from the presentation part of the trial (i.e., the cognitive information needed to guide behavior when the screen is raised; Figure 25.12C,D). Such neurons return to a low level of activity during the actual motor phase of the task, suggesting that they represent working memory and planning (see Chapter 30) rather than the actual movement itself. Delay-specific neurons in the prefrontal cortex are also active in monkeys that have been trained to perform a variant of the delayed response task in which well-learned movements are produced in the absence of any cue. Evidently, these neurons are equally capable of using stored information to guide behavior. Thus, if a monkey is trained to associate eye movements to a particular target with a delayed reward, the delay-associated neurons in the prefrontal cortex will fire during the delay, even if the monkey moves his eyes to the appropriate region of the visual field in the absence of the target.

In addition to maintaining cognitive information during short delays, some neurons in prefrontal cortex also appear to participate directly in longer range planning of sequences of movements. When monkeys are trained to perform a motor sequence, such as turning a joystick to the left, then right, then left again, some neurons in prefrontal cortex fire at a particular point in the sequence (such as the third response), regardless of which movement (e.g., left or right) is made. Prefrontal neurons have also been found that are selective for each position in a learned motor sequence, thus ruling out the possibility that these neurons merely encode task difficulty or proximity to reward as the monkey nears the end of the series of responses. Similar neurons have been found in the supplementary eye field in pre-

Box D

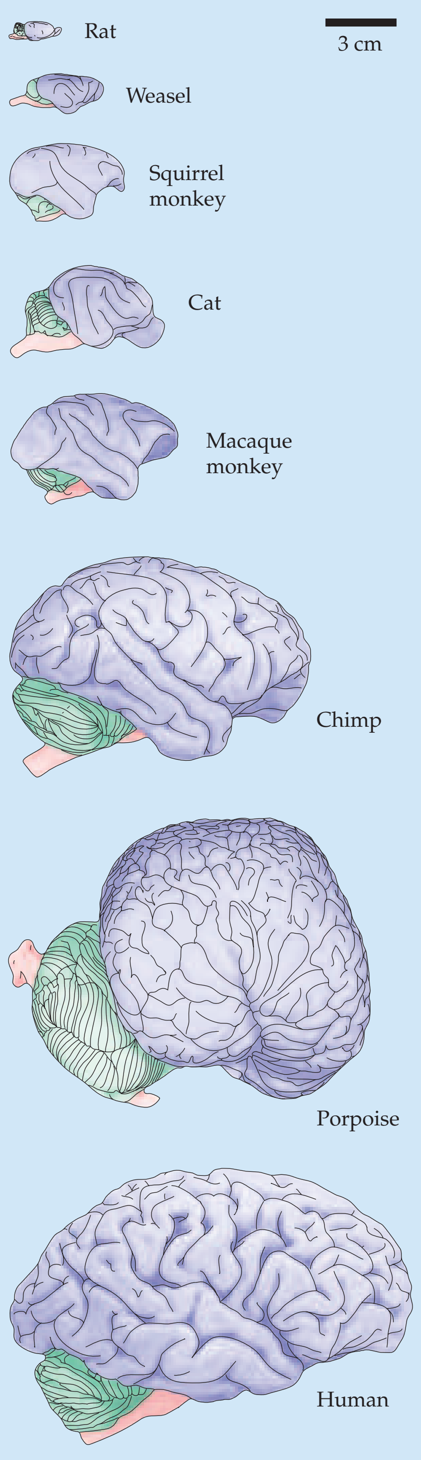
Brain Size and Intelligence

The fact that so much of the brain is occupied by the association cortices raises a fundamental question: does more of it provide individuals with greater cognitive ability? Humans and other animals obviously vary in their talents and predispositions for a wide range of cognitive behaviors. Does a particular talent imply a greater amount of neural space in the service of that function?

Historically, the most popular approach to the issue of brain size and behavior in humans has been to relate the overall size of the brain to a broad index of performance, conventionally measured in humans by "intelligence tests." This way of studying the relationship between brain and behavior has caused considerable trouble. In general terms, the idea that the size of brains from different species reflects intelligence represents a simple and apparently valid idea (see figure). The ratio of brain weight to body weight for fish is 1:5000; for reptiles it is about 1:1500; for birds, 1:220; for most mammals, 1:180; and for humans, it is 1:50. If intelligence is defined as the full spectrum of cognitive performance, surely no one would dispute that a human is more intelligent than a mouse, or that this difference is explained in part by the 3000-fold difference in the size of the brains of these species. Does it follow, however, that relatively small differences in the size of the brain among related species, strains, genders, or individuals—differences that often persist even after correcting for body size—are also a valid measure of cognitive abilities? Certainly no issue in neuroscience has provoked more heated debate than the notion that alleged differences in brain size among races (or the demonstrable differences in brain size between men and women) reflect differences in performance. The passion attending this controversy has been generated not only by the scientific issues involved, but also by the specters of racism and misogyny.

Nineteenth-century enthusiasm for brain size as a simple measure of human performance was championed by some remarkably astute scientists (including Darwin's cousin Francis Galton and the French neurologist Paul Broca), as well as others whose motives and methods are now suspect (see Gould, 1978, 1981 for a fascinating and authoritative commentary). Broca, one of the great neurologists of his day and a gifted observer, not only thought that brain size reflected intelligence, but was of the opinion (as was just about every other nineteenth-century male scientist) that white European males had larger and better developed brains than anyone else. Based on what was known about the human brain in the late nineteenth century, it was perhaps reasonable for Broca to consider it, like the liver or the lung, as an organ having a largely homogeneous function. Ironically, it was Broca himself who laid the groundwork for the modern view that the brain is a heterogeneous collection of highly interconnected but functionally discrete systems (see Chapter 26). Nonetheless, the simplistic nineteenth-century approach to brain size and intelligence has persisted in some quarters well beyond its time.

There are at least two reasons why measures such as brain weight or cranial capacity are not easily interpretable indices of intelligence, even though small observed differences may be statistically valid. First is the obvious difficulty of defining and accurately measuring intelligence , particularly among humans with different educational and cultural backgrounds. Second is the functional diversity and connectional complexity of



the brain. Imagine assessing the relationship between body size and athletic ability, which might be considered the somatic analogue of intelligence. Body weight, or any other global measure of somatic phenotype, would be a woefully inadequate index of athletic ability. Although the evidence would presumably indicate that bigger is better in the context of sumo wrestling or basketball, more subtle somatic features would no doubt be correlated with extraordinary ability in Ping-Pong, gymnastics, or figure skating. The diversity of somatic function vis-à-vis athletic ability confounds the interpretation of any simple measure such as body size.

The implications of this analogy for the brain are straightforward. Any program that seeks to relate brain weight, cranial capacity, or some other measure of overall brain size to individual performance ignores the reality of the brain's functional diversity. Thus, quite apart from the political or ethical probity of attempts to measure "intelligence" by brain size, by the yardstick of modern neuroscience (or simple common sense), this approach will inevitably generate more heat than light. A more rational approach to the issue has become feasible in the last few years, which is to relate the size of measurable regions of known function (the primary visual cortex, for example) to the corresponding functions (visual performance), as well as to cellular features such as synaptic density and dendritic arborization. These correlations have greater promise for exploring the sensible idea that better performance will always be based on more underlying neural machinery.

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frontal cortex that are selective for particular sequences of eye movements. When these regions of prefrontal cortex are inactivated pharmacologically, monkeys lose the ability to execute sequences of movements from memory. These further observations endorse the notion, first inferred from studies of individuals like Phineas Gage, that the frontal lobe contributes specifically to the cognitive functions that use stored information to plan and guide appropriate behavior.

In short, the existence of planning-specific neurons in the frontal cortex of rhesus monkeys, as well as attention-specific cells in the parietal cortex and recognition-specific cells in the temporal cortex, supports the functions of these cortical areas inferred from clinical evidence in humans. Nonetheless, functional localization, whether inferred by examining human patients or by recording single neurons in monkeys, is an imprecise business. The observations summarized here are only a rudimentary guide to thinking about how complex cognitive information is represented and processed in the brain, and how the relevant brain areas and their constituent neurons contribute to such important but still ill-defined qualities as personality, intelligence (Box D), or other cognitive functions that define what it means to be a human being.

Summary

The majority of the human cerebral cortex is devoted to tasks that transcend encoding primary sensations or commanding motor actions. Collectively, the association cortices mediate these cognitive functions of the brain—broadly defined as the ability to attend to, identify, and act meaningfully in response to complex external or internal stimuli. Descriptions of patients with cortical lesions, functional brain imaging of normal subjects, and behavioral and electrophysiological studies of non-human primates have established the general purpose of the major association areas. Thus, parietal association cortex is involved in attention and awareness of the body and the stimuli that act on it; temporal association cortex is involved in the recognition and identification of highly processed sensory information; and frontal association cortex is importantly involved in guiding complex behavior by planning responses to ongoing stimulation (or remembered information), matching such behaviors to the demands of a particular situation. More than any other brain regions, the association areas support the mental processes that make us human.

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Chapter 26

Language and Speech

Overview

One of the most remarkable cortical functions in humans is the ability to associate arbitrary symbols with specific meanings to express thoughts and emotions to ourselves and others by means of written and spoken language. Indeed, the achievements of human culture rest largely upon this kind of communication, and a person who for one reason or another fails to develop a facility for language as a child is severely incapacitated. Studies of patients with damage to specific cortical regions and normal subjects studied by functional brain imaging indicate that linguistic abilities of humans depend on the integrity of several specialized areas of the association cortices in the temporal and frontal lobes. In the vast majority of people, these primary language functions are located in the left hemisphere: the linkages between speech sounds and their meanings are mainly represented in the left temporal cortex, and the circuitry for the motor commands that organize the production of meaningful speech is mainly found in the left frontal cortex. Despite this left-sided predominance for the "lexical" aspects of language, the emotional (affective) content of speech is governed largely by the right hemisphere. Studies of congenitally deaf individuals have shown further that the cortical areas devoted to sign language are the same as those that organize spoken and heard communication. The regions of the brain devoted to language are therefore specialized for symbolic representation and communication, rather than for heard and spoken language as such. Understanding functional localization and hemispheric lateralization of language is especially important in clinical practice. The loss of language is such a devastating blow that neurologists and neurosurgeons make every effort to identify and preserve those cortical areas involved in its comprehension and production. The need to map language functions in patients for the purpose of sparing these regions of the brain has provided another rich source of information about the neural organization of this critical human attribute.

Language Is Both Localized and Lateralized

It has been known for more than a century that two regions in the frontal and temporal association cortices of the left cerebral hemisphere are especially important for normal human language. That language abilities are both localized and lateralized is not surprising; ample evidence of the localization and lateralization of other cognitive functions was reviewed in Chapter 25. The unequal representation of language functions in the two cerebral hemispheres provides an especially compelling example of this phenomenon.

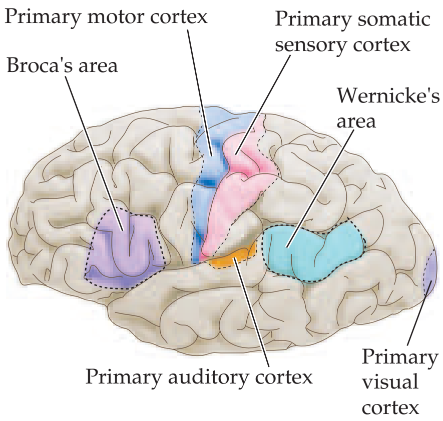

Figure 26.1 Diagram of the major brain areas involved in the comprehension and production of language. The primary sensory, auditory, visual, and motor cortices are indicated to show the relation of Broca's and Wernicke's language areas to these other areas that are necessarily involved in the comprehension and production of speech, albeit in a less specialized way.

Although the concept of lateralization has already been introduced in describing the unequal functions of the parietal lobes in attention and of the temporal lobes in recognizing different categories of objects, it is in language that this idea has been most thoroughly documented. Because language is so important to human beings, its lateralization has given rise to the misleading idea that one hemisphere in humans is actually "dominant" over the other—namely, the hemisphere in which the major capacity for language resides. The true significance of lateralization for language or any other cognitive ability, however, lies in the efficient subdivision of complex functions between the hemispheres, rather than in any superiority of one hemisphere over the other. Indeed, pop psychological dogmas about cortical redundancy notwithstanding, it is a safe presumption is that every region of the brain is doing *something* important.

A first step in the proper consideration of these issues is recognizing that the cortical representation of language is distinct from the circuitry concerned with the motor control of the larynx, pharynx, mouth, and tongue—the structures that produce speech sounds (Box A). Cortical representation is also distinct from, although clearly related to, the circuits underlying the auditory perception of spoken words and the visual perception of written words in the primary auditory and visual cortices, respectively (Figure 26.1). Whereas the neural substrates for language as such depend on these essential motor and sensory functions, the regions of the brain that are specifically devoted to language transcend these more basic elements. The main concern of the areas of cortex that represent language is using of a system of symbols for purposes of communication—spoken and heard, written and read, or, in the case of sign language, gestured and seen. Thus, the essential function of the cortical language areas, and indeed of language, is symbolic representation. Obedience to a set of rules for using these symbols (called grammar), ordering them to generate useful meanings (called syntax), and giving utterances the appropriate emotional valence (called prosody), are all important and readily recognized regardless of the particular mode of representation and expression.

Given the profound biological and social importance of communication among the members of a species, it is not surprising that other animals communicate in ways that, while grossly impoverished compared to human language, nonetheless suggest the sorts of communicative skills and interactions from which human language evolved in the brains of our prehominid ancestors (Box B).

Aphasias

The distinction between language and the related sensory and motor capacities on which it depends was first apparent in patients with damage to specific brain regions. Clinical evidence of this sort showed that the ability to move the muscles of the larynx, pharynx, mouth, and tongue can be compromised without abolishing the ability to use spoken language to communicate (even though a motor deficit may make communication difficult). Similarly, damage to the auditory pathways can impede the ability to hear without interfering with language functions per se (as is obvious in individuals who have become partially or wholly deaf later in life). Damage to specific brain regions, however, can compromise essential language functions while leaving the sensory and motor infrastructure of verbal communication intact. These syndromes, collectively referred to as **aphasias**, diminish or abolish the ability to comprehend and/or to produce *language*, while sparing

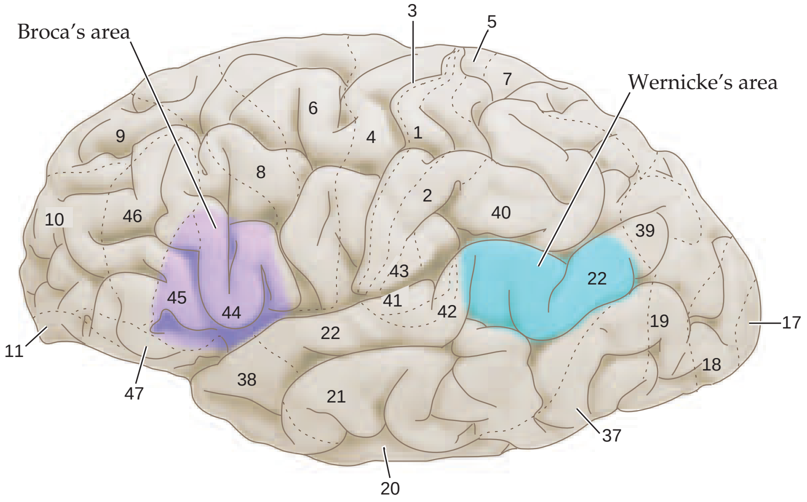

Figure 26.2 The relationship of the major language areas to the classical cytoarchitectonic map of the cerebral cortex. As discussed in Chapter 25, about 50 histologically distinct regions (cytoarchitectonic areas) have been described in the human cerebral cortex. Whereas primary sensory and motor functions are sometimes coextensive with these areas, more general cognitive functions like attention, identification, and planning typically encompass a number of different cytoarchitectonic areas in one or more cortical lobes. The language functions described by Broca and Wernicke are associated with at least three of the cytoarchitectonic areas defined by Brodmann (area 22, at the junction of the parietal and temporal lobes [Wernicke's area]; and areas 44 and 45, in the ventral and posterior region of the frontal lobe [Broca's area]), and are not coextensive with any of them.

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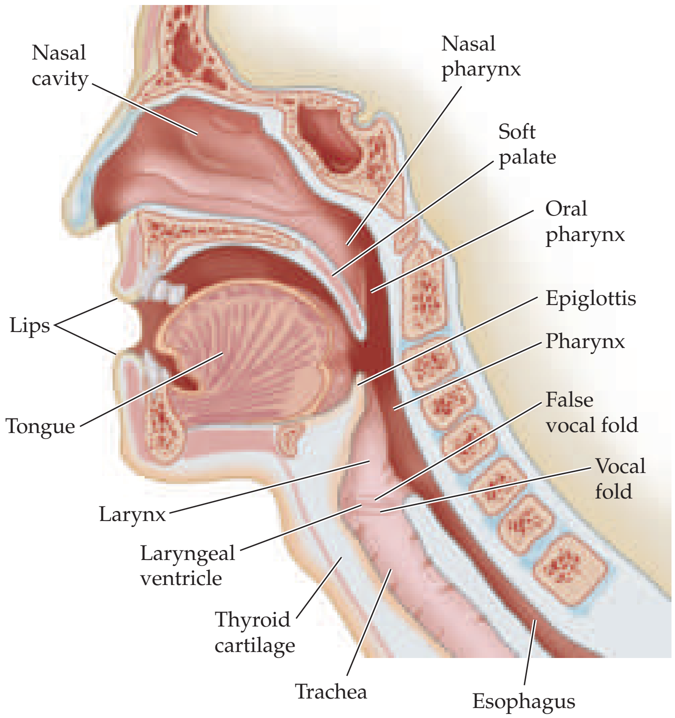
the ability to perceive the relevant stimuli and to produce intelligible words. Missing in these patients is the capacity to recognize or employ the symbolic value of words, thus depriving such individuals of the linguistic understanding, grammatical and syntactical organization, and appropriate intonation that distinguishes language from nonsense (Box C).

The localization of language function to a specific region (and to some degree a hemisphere) of the cerebrum is usually attributed to the French neurologist Paul Broca and the German neurologist Carl Wernicke, who made their seminal observations in the late 1800s. Both Broca and Wernicke examined the brains of individuals who had become aphasic and later died. Based on correlations of the clinical picture and the location of the brain damage, Broca suggested that language abilities were localized in the ventroposterior region of the frontal lobe (Figures 26.1 and 26.2). More importantly, he observed that the loss of the ability to produce meaningful language—as opposed to the ability to move the mouth and produce words—was usually associated with damage to the left hemisphere. "*On parle avec l'hemisphere gauche*," Broca concluded. The preponderance of aphasic syndromes associated with damage to the left hemisphere has supported his claim that one speaks with the left hemisphere, a conclusion amply confirmed by a variety of modern studies using functional imaging (albeit with some important caveats, discussed later in the chapter).

Although Broca was basically correct, he failed to grasp the limitations of thinking about language as a unitary function localized in a single cortical region. This issue was better appreciated by Wernicke, who distinguished between patients who had lost the ability to comprehend language and those who could no longer produce language. Wernicke recognized that some aphasic patients do not understand language but retain the ability to produce utterances with reasonable grammatical and emotional content. He concluded that lesions of the posterior and superior temporal lobe on the left side tend to result in a deficit of this sort. In contrast, other patients continue to comprehend language but lack the ability to organize or control the linguistic content of their response. Thus, they produce nonsense syllables, transposed words, and utter grammatically incomprehensible phrases. These deficits are associated with damage to the posterior and inferior region of the left frontal lobe, an area that Broca emphasized as an important substrate for language (see Figures 26.1 and 26.2).

Box A

Speech



The organs that produce speech include the lungs, which serve as a reservoir of air; the larynx, which is the source of the periodic stimulus quality of "voiced" sounds; and the pharynx, oral, and nasal cavities and their included structures (e.g., tongue, teeth, and lips), which modify (or filter) the speech sounds that eventually emanate from the speaker. The fundamentally correct idea that the larynx is the "source" of speech sounds and the rest of the vocal tract acts as a filter that modulates the sound energy of the source is an old one, having been proposed by Johannes Mueller in the nineteenth century.

Although the physiological details are complex, the general operation of the vocal apparatus is simple. Air expelled from the lungs accelerates as it passes through a constricted opening between the **vocal folds** ("vocal cords") called the glottis, thus decreasing the pressure in the air stream (according Bernoulli's principle). As a result, the vocal folds come together until the pressure buildup in the lungs forces them open again. The ongoing repetition of this process results in an oscillation of sound wave pressure, the frequency of which is determined primarily by the muscles that control the tension on the vocal cords. The frequencies of these oscillations—which are the basis of voiced speech sounds—range from about 100 to about 400 Hz, depending on the gender, size, and age of the speaker.

The larynx has many other consequential effects on the speech signal that create additional speech sounds. For instance, the vocal folds can open suddenly to produce what is called a *glottal stop* (as in the beginning of the exclamation "Idiot!"). Alternatively, the vocal folds can hold an intermediate position for the production of consonants such as *h*, or they can be completely open for "unvoiced" consonants such as *s* or *f* (i.e., speech sounds that don't have the periodic quality derived from vocal fold oscillations). In short, the larynx is important in the production of virtually all vocal sounds.

The vocal system can be thought of as a sort of musical instrument capable of extraordinary subtlety and exquisite modulation. As in the sound produced by a musical instrument, however, the primary source of oscillation (e.g., the reed of a clarinet or the vocal folds in speech) is hardly the whole story. The entire pathway between the vocal folds and the lips (and nostrils) is equally critical in determining speech sounds, as is the structure of a musical instrument. The key determinants of the sound that emanates from an instrument are its natural resonances, which shape or filter the sound pressure oscillation. For the vocal tract, the resonances that modulate the air stream generated by the larynx are called **formants**. The resonance fre-

As a consequence of these early observations, two rules about the localization of language have been taught ever since. The first is that lesions of the left frontal lobe in a region referred to as **Broca's area** affect the ability to *produce* language efficiently. This deficiency is called **motor** or **expressive** quency of the major formant arises from the fact that the approximate length of the vocal tract is 17 cm, which is the quarter wavelength of a 68-cm sound wave; quarter wavelengths determine the resonances of pipes open at one end, which is essentially what the vocal tract is. Since the speed of sound is about 33,500 cm/sec, the lowest resonance frequency of an open tube or pipe of this length will be 33,500/68 or about 500 Hz; additional resonant frequencies will occur at the odd harmonics of this major formant (e.g., 1500 Hz, 2500 Hz, etc.). The result of these physical facts about the vocal tract is that any power in the laryngeal source at these formant frequencies will be reinforced, and any other power will, in varying degrees, be filtered out. Of course, this general statement is complicated by the further fact that the shape of the vocal tract changes to produce different speech sounds. Thus, in addition to the effects of the larynx, specific speech sounds are generated by dynamic effects imposed by the configuration of the rest of the vocal tract.

In any given language, the basic speech sounds are called **phonemes**. (The sound stimuli as such are referred to as **phones**.) Phonemes are used to make up syllables, which are used in turn to make up words, which are used to create sentences. There are about 40 phonemes in English, and these are about equally divided between vowel and consonant speech sounds. Vowel sounds are by and large the voiced (periodic) elements of speech (i.e., the elemental sounds in any language generated by the oscillation of the vocal cords). In contrast, consonant sounds involve rapid changes in the sound signal and are more complex. In English, consonants begin and/or end syllables, each of which entails a vowel sound. Consonant sounds are categorized according to the site in the vocal tract that determines them (the *place of articulation*), or the physical way they are generated (the *manner of articulation*). With respect to place, there are labial consonants (such as *p* and *b*), dental consonants (*f* and *v*), palatal consonants (*sh*), and glottal consonants (*h*) (among many others). With respect to manner, there are plosive, fricative, nasal, liquid, and semivowel consonants. Plosives are produced by blocking the flow of air somewhere in the vocal tract, fricatives by producing turbulence, nasals by directing the flow of air through the nose, and so on.

A further variation on the use of consonants is found in the "click languages" of southern Africa, of which about 30 survive today. Each of these languages has 4–5 different click sounds that are double consonants (the consonant equivalent of dipthongs) made by sucking the tongue down from the roof of the mouth.

It should be obvious then that speech stimuli are enormously complex (there are more than 200 phonemes in human languages). To make matters worse, Alvin Liberman, working at the Haskins Laboratory at Yale University, showed that there is no one-to-one correspondence between phonemes (as defined above) and phones (i.e., the specific acoustic elements in speech). Because speech sounds changes continuously, they cannot be split up into discrete segments, as the concept of phonemes implies. This fact is now recognized as a fundamental problem that undermines any strictly phonemic approach to language. Moreover, the phones for different vowels (or at least the formants) overlap in natural speech of men, women, and children. Evidence from studies of illiterates suggests that phonemes are probably more related to learning how to read and spell than to actually hearing speech, implying that syllables or words are much better candidates for the natural units of speech perception.

Given this complexity, it is remarkable that we can communicate so readily. A clue to the obvious success of humans in this task is computer-based speech recognition programs. These programs achieve the very substantial success they currently enjoy by virtue of prolonged empirical training rather than in the *a priori* application of any logical rules.

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aphasia, also known as **Broca's aphasia**. (Such aphasias must be specifically distinguished from *dysarthria*, which is the inability to move the muscles of the face and tongue that mediate speaking.) The deficient motor-planning aspects of expressive aphasias accord with the complex motor functions of

Box B

Do Other Animals Have Language?

Over the centuries, theologians, natural philosophers, and a good many modern neuroscientists have argued that language is uniquely human, this extraordinary behavior being seen as setting us qualitatively apart from our fellow animals. However, the gradual accumulation of evidence during the last 75 years demonstrating highly sophisticated systems of communication in species as diverse as bees, birds, monkeys, and whales has made this point of view increasingly untenable, at least in a broad sense (see Box B in Chapter 23). Until recently, however, human language *has* appeared unique in the ability to associate specific meanings with arbitrary symbols, ad infinitum. In the dance of the honeybee described so beautifully by Karl von Frisch, for example, each symbolic movement made by a foraging bee that returns to the hive encodes only a single meaning, whose expression and appreciation has been hardwired into the nervous systems of the actor and the respondents.

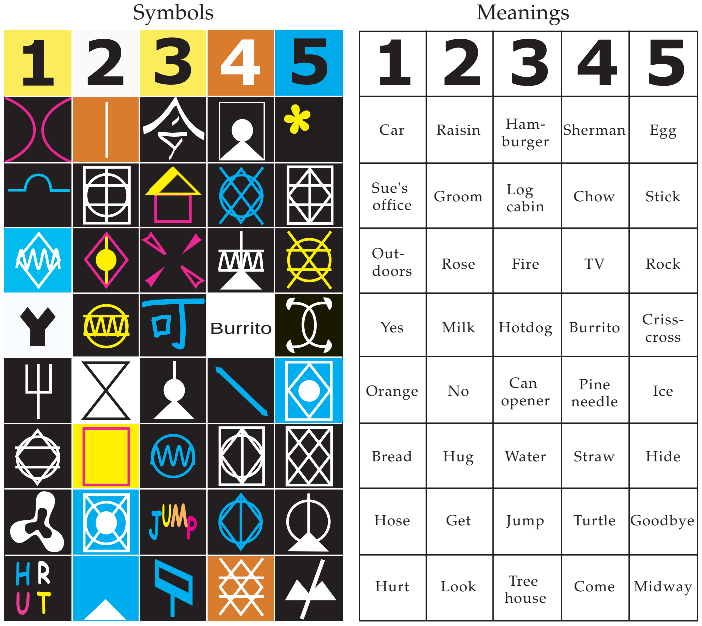
A series of controversial studies in great apes, however, have indicated that the rudiments of the human symbolic communication are evident in the behavior of our closest relatives. Although early efforts were sometimes patently misguided (initial attempts to teach chimpanzees to speak were without merit simply because these animals lack the necessary vocal apparatus), modern work on this issue has shown that if chimpanzees are given the means to communicate symbolically, they demonstrate some surprising talents. While techniques have varied, most psychologists who study chimps have used some form of manipulable symbols that can be arranged to express ideas in an interpretable manner.

For example, chimps can be trained to manipulate tiles or other symbols (such as the gestures of sign language) to represent words and syntactical constructs, allowing them to communicate simple demands, questions, and even spontaneous expressions. The most remarkable results have come from increasingly sophisticated work with chimps using keyboards with a variety of symbols (Figure A). With appropriate training, chimps can choose from as many as 400 different symbols to construct expressions, allowing the researchers to have something resembling a rudimentary conversation with their charges. The more accomplished of these animals are alleged to have "vocabularies" of several thousand words or phrases, equivalent to a child 3 or 4 years of age (how they use these words compared to a child, however, is much less impressive).

Given the challenge this work presents to some long-held beliefs about the uniqueness of human language, it is not surprising that these claims continue to stir up debate and are not universally accepted. Nonetheless, the issues raised certainly deserve careful consideration by anyone interested in human language abilities and how our remarkable symbolic skills may have evolved from the communicative capabilities of our ancestors. The pressure for the evolution of some form of symbolic communication in great apes seems clear enough. Ethologists studying chimpanzees in the wild have described extensive social communication based on gestures, the manipulation of objects, and facial expressions. This intricate social intercourse is likely to be the antecedent of human language; one need only think of the importance of gestures and facial expressions as ancillary aspects of our own speech to appreciate this point. (The sign language studies described later in the chapter are also pertinent here.)

Whether the regions of the temporal, parietal, and frontal cortices that support human language also serve these sym-

(A)



1	2	3	4	5
Car	Raisin	Hamburger	Sherman	Egg
Sue's office	Groom	Log cabin	Chow	Stick
Outdoors	Rose	Fire	TV	Rock
Yes	Milk	Hotdog	Burrito	Criss-cross
Orange	No	Can opener	Pine needle	Ice
Bread	Hug	Water	Straw	Hide
Hose	Get	Jump	Turtle	Goodbye
Hurt	Look	Tree house	Come	Midway

Section of keyboard showing lexical symbols used to study symbolic communication in great apes. (From Savage-Rumbaugh et al., 1998.)

(B)

The brains of great apes are remarkably similar to those of humans, including regions that, in humans, support language. The areas comparable to Broca's area and Wernicke's area are indicated.

bolic functions in the brains of great apes (Figure B) is an important question that remains to be tackled. In addition, field studies of vervets and other monkey species have shown that the alarm calls of these animals differ according to the nature of the threat. Thus, ethologists Dorothy Cheney and Robert Seyfarth found that a specific alarm call uttered when a vervet monkey spotted a leopard caused nearby vervets to take to the trees; in contrast, the alarm call given when a monkey saw an eagle caused other monkeys to look skyward. More recent studies of monkey calls by Marc Hauser and his collaborators have greatly extended this sort of work.

Although much uncertainty remains, in light of this evidence only someone given to extraordinary anthropocentrism would continue to argue that symbolic communication is a uniquely human attribute. In the end, it may turn out to be that human language, for all its seeming complexity, is based on the same general scheme of inherent and acquired neural associations that appears to be the basis of any animal communication.

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the posterior frontal lobe and its proximity to the primary motor cortex already discussed (see Chapters 15 and 25).

The second rule is that damage to the left temporal lobe causes difficulty *understanding* spoken language, a deficiency referred to as **sensory** or **receptive aphasia**, also known as **Wernicke's aphasia**. (Deficits of reading and writing—*alexias* and *agraphias*—are separate disorders that can arise from damage to related but different brain areas; most aphasics, however, also have difficulty with these closely linked abilities as well.) Receptive aphasia generally reflects damage to the auditory association cortices in the posterior temporal lobe, a region referred to as **Wernicke's area**.

A final broad category of language deficiency syndromes is **conduction aphasia**. These disorders arise from lesions to the pathways connecting the relevant temporal and frontal regions, such as the arcuate fasciculus in the subcortical white matter that links Broca's and Wernicke's areas. Interruption of this pathway may result in an inability to produce appropriate responses to heard communication, even though the communication is understood.

In a classic Broca's aphasia, the patient cannot express himself appropriately because the organizational aspects of language (its grammar and syntax) have been disrupted, as shown in the following example reported by Howard Gardner (who is the interlocutor). The patient was a 39-year-old Coast Guard radio operator named Ford who had suffered a stroke that affected his left posterior frontal lobe.

> 'I am a sig…no…man…uh, well,…again.' These words were emitted slowly, and with great effort. The sounds were not clearly articulated; each syllable as uttered harshly, explosively, in a throaty voice. With practice, it was possible to understand him, but at first I encountered considerable difficulty in this. 'Let me help you,' I interjected. 'You were a signal…' 'A sig-nal man…right,' Ford completed my phrase triumphantly. 'Were you in the Coast Guard?' 'No, er, yes, yes, …ship…Massachu…chusetts…Coastguard …years.' He raised his hands twice, indicating the number nineteen. 'Oh, you were in the Coast Guard for nineteen years.' 'Oh…boy…right…right,' he replied. 'Why are you in the hospital, Mr. Ford?' Ford looked at me strangely, as if to say, Isn't it patently obvious? He pointed to his paralyzed arm and said, 'Arm no good,' then to his mouth and said, 'Speech…can't say…talk, you see.'
>
> Howard Gardner, 1974.
> (*The Shattered Mind: The Person after Brain Damage*, pp. 60–61.)

In contrast, the major difficulty in Wernicke's aphasia is putting together objects or ideas and the words that signify them. Thus, in a Wernicke's aphasia, speech is fluent and well structured, but makes little or no sense because words and meanings are not correctly linked, as is apparent in the following example (again from Gardner). The patient in this case was a 72-year-old retired butcher who had suffered a stroke affecting his left posterior temporal lobe.

> Boy, I'm sweating, I'm awful nervous, you know, once in a while I get caught up, I can't get caught up, I can't mention the tarripoi, a month ago, quite a little, I've done a lot well, I impose a lot, while, on the other hand, you know what I mean, I have to run around, look it over, trebbin and all that sort of stuff. Oh sure, go ahead, any old think you want. If I could I would. Oh, I'm taking the word the wrong way to say, all of the barbers here whenever they stop you it's going around and around, if you know what I mean, that is tying and tying for repucer, repuceration, well, we were trying the best that we could while another time it was with the beds over there the same thing…
>
> Ibid., p. 68.

The major differences between these two classical aphasias are summarized in Table 26.1.

Despite the validity of Broca's and Wernicke's original observations, the classification of language disorders is considerably more complex. An effort to refine the nineteenth-century categorization of aphasias was undertaken

TABLE 26.1
Characteristics of Broca's and Wernicke's Aphasias

Broca's aphasia[a]	*Wernicke's aphasia*[b]
Halting speech	Fluent speech
Tendency to repeat phrases or words (perseveration)	Little spontaneous repetition
Disordered syntax	Syntax adequate
Disordered grammar	Grammar adequate
Disordered structure of individual words	Contrived or inappropriate words
Comprehension intact	Comprehension not intact

[a] Also called motor, expressive, or production aphasia
[b] Also called sensory or receptive aphasia

Box C

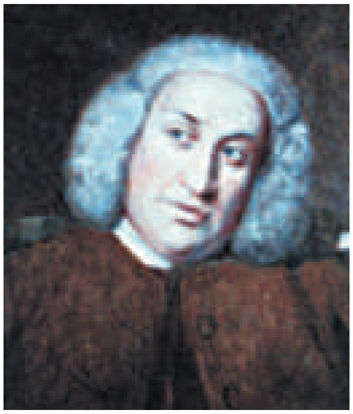
Words and Meaning

When Samuel Johnson (Figure A) compiled his *Dictionary of English Language* in 1755 under the sponsorship of Oxford University, he defined only 43,500 entries. The current *Oxford English Dictionary*, a lineal descendant of Johnson's seminal work and most recently revised in the 1980s, contains over 500,000 definitions! This quantitative difference is not the result of an increase in the number of English words since the eighteenth century, but rather is an indication of the difficulty collecting the enormous number of words we use in daily communication; the average college-educated speaker of English is said to have a working vocabulary of more than 100,000 words.

Using words appropriately is made even more difficult by the fact that word meanings are continually changing, and by the enormous ambiguity of the words we do use. There is far more to a lexicon—be it a dictionary or a region of the left temporal cortex—than simply attaching meanings to words. Even when the meaning of a word is known, it must be understood in a particular context (Figure B) and used according to the rules of grammar and syntax in order to produce effective communication.

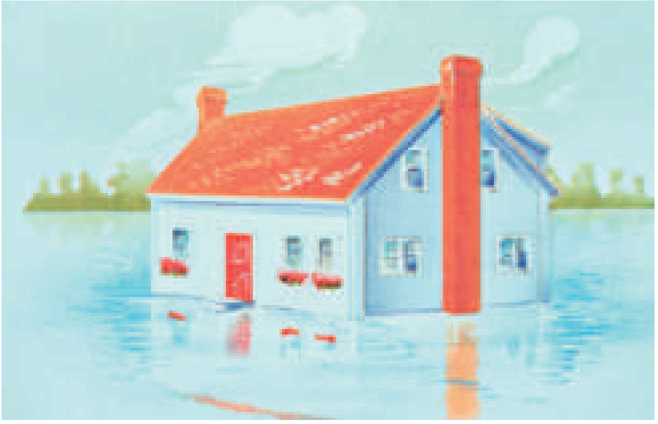
From the points of view of both neuroscience and linguistics, two related questions about words and grammar (i.e., the rules for putting words together to form sentences) are especially germane in relation to this chapter. First, what is the nature of the neural machinery that allows us to learn language? And second, why do humans have such a profound drive to learn language? The major twentieth-century figure who has grappled with these questions is linguist Noam Chomsky, working at the Massachusetts Institute of Technology. Chomsky, while not interested in brain structure has argued that the complexity of language is such that it cannot simply be learned. He therefore proposed that language must be predicated on a "universal grammar" laid down in the evolution of our species. Although this argument is undoubtedly correct (the basic neural machinery for language, like all aspects of brain circuitry that support adult behavior, is indeed constructed during the normal development of each individual, primarily as a result of inheritance; see Chapters 22 and 23), Chomsky's eschewing of neurobiology avoids the central question of how, in evolutionary or developmental terms, this machinery comes to be and how it encodes words and strings them together into meaningful sentences. Whatever the mechanisms eventually prove to be, much of the language we use is obviously learned by making neuronal associations between arbitrary symbols and the objects, concepts, and interrelationships they signify in the real world. As such, human language provides a rich source for understanding how the relevant parts of the human cortex and their constituent neurons work to produce the enormous facility for making associations, which appears to be a fundamental (perhaps *the* fundamental) aspect of all cortical functions.

(A)



Samuel Johnson

(B)



The importance of context. When a person says "I'm going to our house on the lake," the meaning of the expression obviously depends on usage and context, rather than on the literal structure of the sentence uttered. This example indicates the enormous complexity of the task we all accomplish routinely. How this is done, even in principle, remains a central puzzle in language. (From Miller, 1991.)

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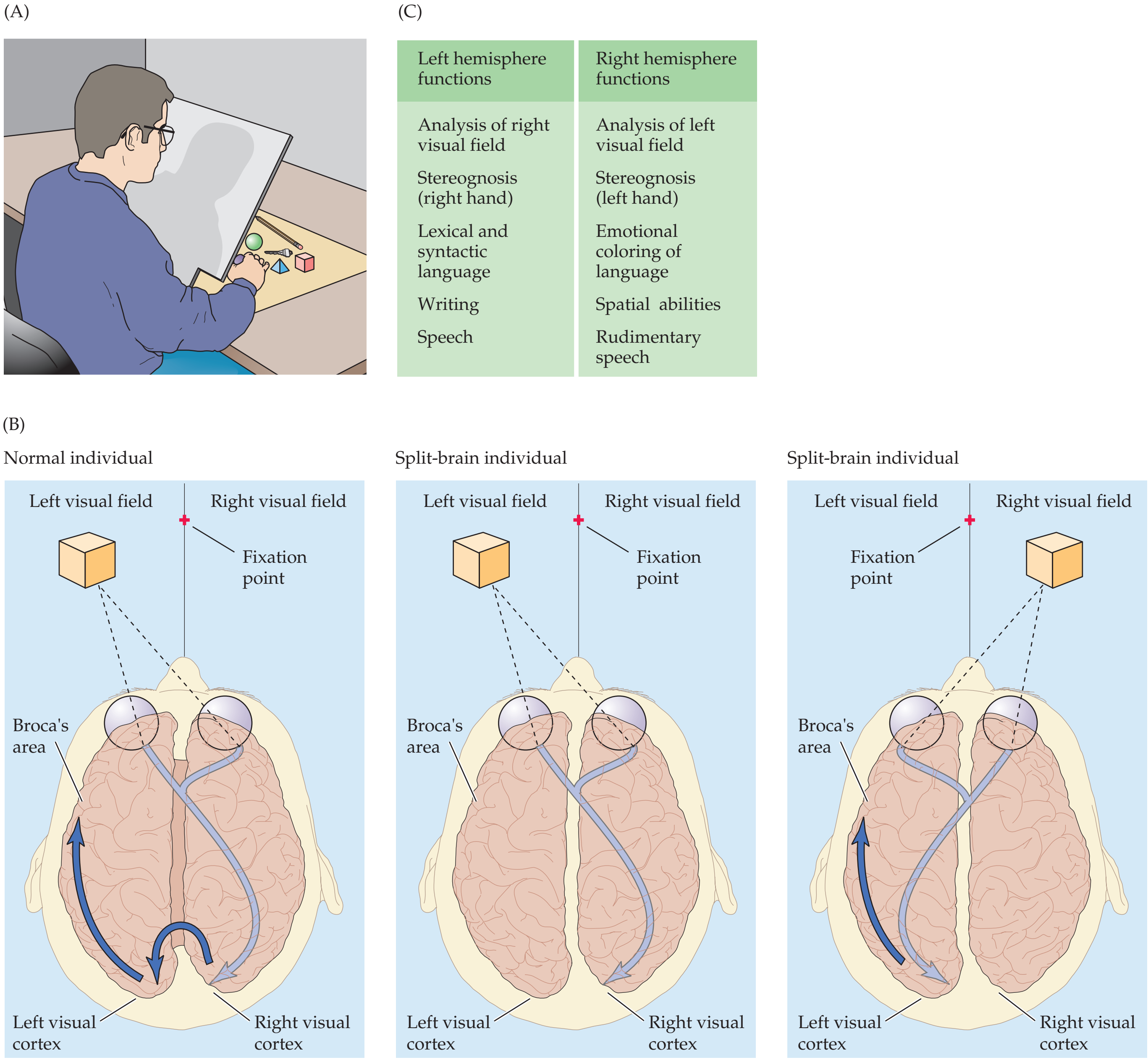
by the American neurologist Norman Geschwind during the 1950s and early 1960s. Based on clinical and anatomical data from a large number of patients and on the better understanding of cortical connectivity gleaned by that time from animal studies, Geschwind concluded correctly that several other regions of the parietal, temporal, and frontal cortices are critically involved in human linguistic capacities. Basically, he showed that damage to these additional areas results in identifiable, if more subtle, language deficits. His clarification of the definitions of language disorders has been largely confirmed by functional brain imaging in normal subjects, and remains the basis for much contemporary clinical work on language and aphasias.

A Dramatic Confirmation of Language Lateralization

Until the 1960s, observations about language localization and lateralization were based primarily on patients with brain lesions of varying severity, location, and etiology. The inevitable uncertainties of clinical findings allowed skeptics to argue that language function (or other complex cognitive functions) might not be lateralized (or even localized) in the brain. Definitive evidence supporting the inferences from neurological observations came from studies of patients whose corpus callosum and anterior commissure had been severed as a treatment for medically intractable epileptic seizures. (Recall that a certain fraction of severe epileptics are refractory to medical treatment, and that interrupting the connection between the two hemispheres remains an effective way of treating epilepsy in highly selected patients; see Box C in Chapter 24). In such patients, investigators could assess the function of the two cerebral hemispheres *independently*, since the major axon tracts that connect them had been interrupted. The first studies of these so-called **split-brain patients** were carried out by Roger Sperry and his colleagues at the California Institute of Technology in the 1960s and 1970s, and established the hemispheric lateralization of language beyond any doubt; this work also demonstrated many other functional differences between the left and right hemispheres (Figure 26.3) and continues to stand as an extraordinary contribution to the understanding of brain organization.

Figure 26.3 Confirmation of hemispheric specialization for language obtained by studying individuals in whom the connections between the right and left hemispheres have been surgically divided. (A) Single-handed, vision-independent stereognosis can be used to evaluate the language capabilities of each hemisphere in split-brain patients. Objects held in the right hand, which provides somatic sensory information to the left hemisphere, are easily named; objects held in the left hand, however, are not readily named by these patients. (B) Visual stimuli or simple instructions can be given independently to the right or left hemisphere in normal and split-brain individuals. Since the left visual field is perceived by the right hemisphere (and vice versa; see Chapter 11), a briefly presented (*tachistoscopic*) instruction in the left visual field is appreciated only by the right brain (assuming that the individual maintains fixation on a mark in the center of the viewing screen). In normal subjects, activation of the right visual cortex leads to hemispheric transfer of visual information via the corpus callosum to the left hemisphere. In split-brain patients, information presented to the left visual field cannot reach the left hemisphere, and patients are unable to produce a verbal report regarding the stimuli. However, such patients *are* able to provide a verbal report of stimuli presented to the right visual field. A wide range of hemispheric functions can be evaluated using this tachistoscopic method, even in normal subjects. The list (above right) enumerates some of the different functional abilities of the left and right hemispheres, as deduced from a variety of behavioral tests in split-brain patients.

To evaluate the functional capacity of each hemisphere in split-brain patients, it is essential to provide information to one side of the brain only. Sperry, Michael Gazzaniga (a key collaborator in this work), and others devised several simple ways to do this, the most straightforward of which was to ask the subject to use each hand independently to identify objects without any visual assistance (Figure 26.3A). Recall from Chapter 8 that somatic sensory information from the right hand is processed by the left hemisphere, and vice versa. By asking the subject to describe an item being manipulated by one hand or the other, the language capacity of the relevant hemisphere could be examined. Such testing showed clearly that the two hemispheres differ in their language ability (as expected from the post-mortem correlations described earlier).


(A)
(C)
(B)
Normal individual
Split-brain individual
Split-brain individual
Left visual field
Right visual field
Fixation point
Broca's area
Left visual cortex
Right visual cortex

Left hemisphere functions	Right hemisphere functions
Analysis of right visual field	Analysis of left visual field
Stereognosis (right hand)	Stereognosis (left hand)
Lexical and syntactic language	Emotional coloring of language
Writing	Spatial abilities
Speech	Rudimentary speech

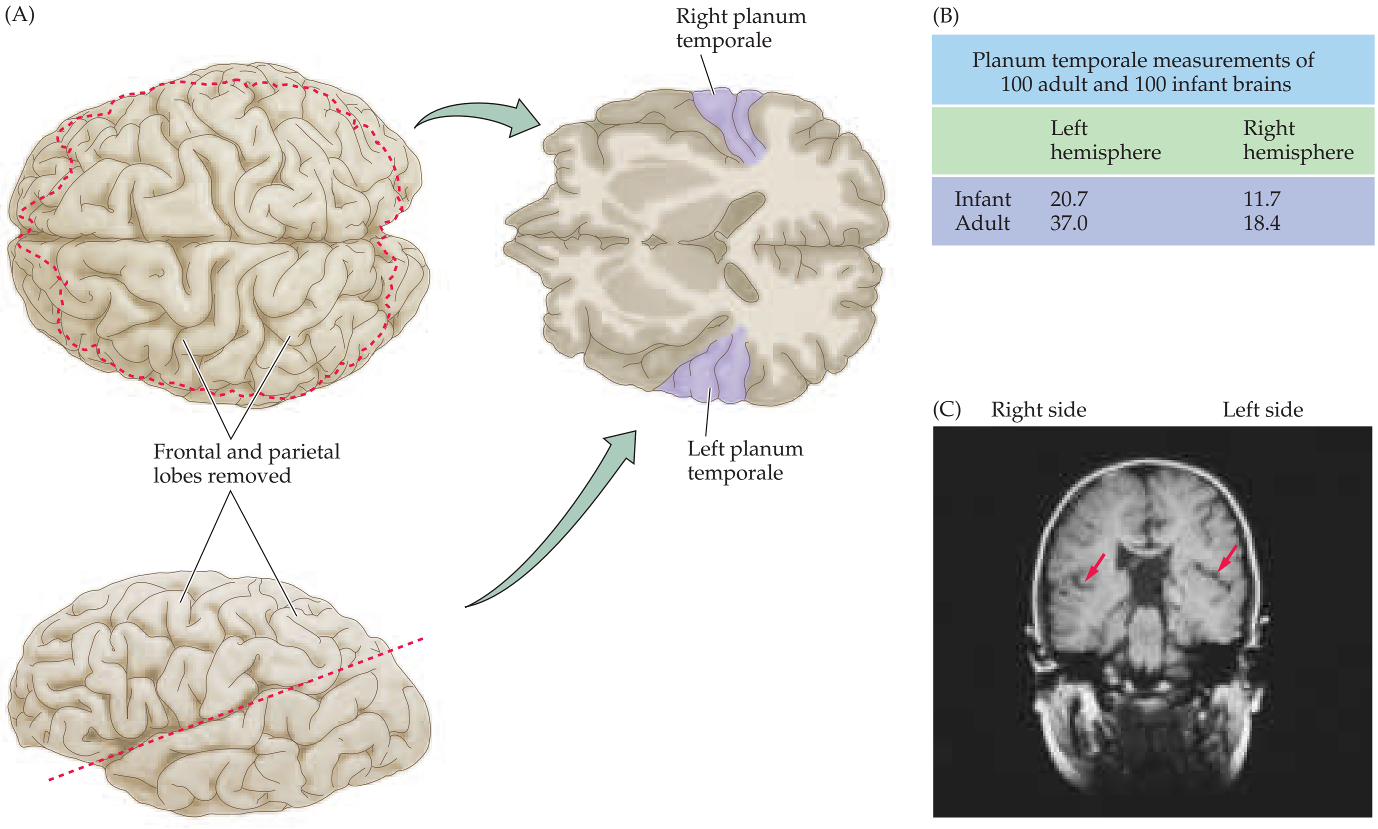
Using the left hemisphere, split-brain patients were able to name objects held in the right hand without difficulty. In contrast, and quite remarkably, an object held in the left hand could not be named! Using the right hemisphere, subjects could produce only an indirect description of the object that relied on rudimentary words and phrases rather than the precise lexical symbol for the object (for instance, “a round thing” instead of “a ball”), and some could not provide any verbal account of what they held in their left hand. Observations using special techniques to present visual information to the hemispheres independently (a method called *tachistoscopic presentation*; Figure 26.3B) showed further that the left hemisphere can respond to written commands, whereas the right hemisphere can typically respond only to nonverbal stimuli (e.g., pictorial instructions, or, in some cases, rudimentary written commands). These distinctions reflect broader hemispheric differences summarized by the statement that the left hemisphere in most humans is specialized for (among other things) the verbal and symbolic processing important in communication, whereas the right hemisphere is specialized for (among other things) visuospatial and emotional processing (see Figure 26.3).

The ingenious work of Sperry and his colleagues on split-brain patients put an end to the century-long controversy about language lateralization; in most individuals, the left hemisphere is unequivocally the seat of the major language functions (although see Box D). It would be wrong to suppose, however, that the right hemisphere has no language capacity. As noted, in some individuals the right hemisphere can produce rudimentary words and phrases, and it is normally the source of emotional coloring of language (see below and Chapter 28). Moreover, the right hemisphere in many split-brain patients understands language to a modest degree, since these patients can respond to simple visual commands presented tachistoscopically in the left visual field. Consequently, Broca’s conclusion that we speak with our left brain is not strictly correct; it would be more accurate to say that we understand language and speak very much better with the left hemisphere than with the right, and thus that the contributions of the two hemispheres to the overall goals of communication are different.

Anatomical Differences between the Right and Left Hemispheres

The differences in language function between the left and right hemispheres have naturally inspired neurologists and neuropsychologists to find a structural correlate of this behavioral lateralization. One hemispheric difference that has received much attention over the years was identified in the late 1960s by Norman Geschwind and his colleagues at Harvard Medical School, who found an asymmetry in the superior aspect of the temporal lobe known as the **planum temporale** (Figure 26.4). This area was significantly larger on the left side in about two-thirds of human subjects studied postmortem, a difference that has also been found in higher apes, but not in other primates.

Because the planum temporale is near (although certainly not congruent with) the regions of the temporal lobe that contain cortical areas essential to language (i.e., Wernicke’s area and other auditory association areas), it was initially suggested that this leftward asymmetry reflected the greater involvement of the left hemisphere in language. Nonetheless, these anatomical differences in the two hemispheres of the brain, which are recognizable at birth, are unlikely to be an anatomical correlate of the lateralization of language functions. The fact that a detectable planum asymmetry is present in only 67% of human brains, whereas the preeminence of language in the left



Planum temporale measurements of 100 adult and 100 infant brains		
	Left hemisphere	Right hemisphere
Infant	20.7	11.7
Adult	37.0	18.4

Figure 26.4 Asymmetry of the right and left human temporal lobes. (A) The superior portion of the brain has been removed as indicated to reveal the dorsal surface of the temporal lobes in the right-hand diagram (which presents a dorsal view of the horizontal plane). A region of the surface of the temporal lobe called the planum temporale is significantly larger in the left hemisphere of most (but far from all) individuals. (B) Measurements of the planum temporale in adult and infant brains. The mean size of the planum temporale is expressed in arbitrary planimetric units to get around the difficulty of measuring the curvature of the gyri within the planum. The asymmetry is evident at birth and persists in adults at roughly the same magnitude (on average, the left planum is about 50% larger than the right). (C) A magnetic resonance image in the frontal plane, showing this asymmetry (arrows) in a normal adult subject.

hemisphere is evident in 97% of the population, argues that this association has some other cause. The structural correlate of the functional left–right differences in hemispheric language abilities, if indeed there is one at a gross anatomical level, is simply not clear, as is the case for the lateralized hemispheric functions described in Chapter 25.

Mapping Language Functions

The pioneering work of Broca and Wernicke, and later Geschwind and Sperry, clearly established differences in hemispheric function. Several techniques have since been developed that allow hemispheric attributes to be assessed in neurological patients with an intact corpus callosum, and in normal subjects.

One method that has long been used for the clinical assessment of language lateralization was devised in the 1960s by Juhn Wada at the Montreal Neurological Institute. In the so-called Wada test, a short-acting anesthetic (e.g., sodium amytal) is injected into the left carotid artery; this procedure transiently "anesthetizes" the left hemisphere and thus tests the functional capabilities of the affected half of the brain. If the left hemisphere is indeed "dominant" for language, then the patient becomes transiently aphasic while carrying out an ongoing verbal task like counting. The anesthetic is rapidly diluted by the circulation, but not before its local effects on the hemisphere on the side of the injection can be observed. Since this test is potentially dangerous, its use is limited to neurological and neurosurgical patients.

Box D

Language and Handedness

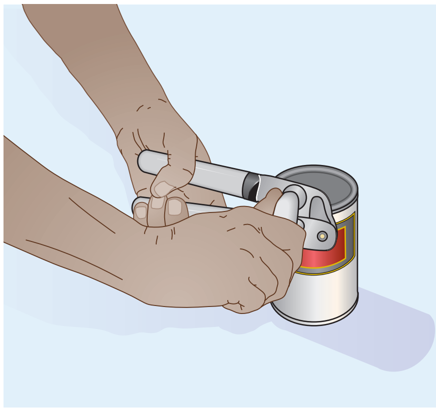
Approximately 9 out of 10 people are right-handed, a proportion that appears to have been stable over thousands of years and across all cultures in which handedness has been examined. Handedness is usually assessed by having individuals answer a series of questions about preferred manual behaviors, such as “Which hand do you use to write?”; “Which hand do you use to throw a ball?”; or “Which hand do you use to brush your teeth?” Each answer is given a value, depending on the preference indicated, providing a quantitative measure of the inclination toward right- or left-handedness. Anthropologists have determined the incidence of handedness in ancient cultures by examining artifacts; the shape of a flint ax, for example, can indicate whether it was made by a right- or left-handed individual. Handedness in antiquity has also been assessed by examining the incidence of figures in artistic representations who are using one hand or the other. Based on this evidence, the human species appears always to have been a right-handed one. Handedness, or its equivalent, is not peculiar to humans; many studies have demonstrated paw preference in animals ranging from mice to monkeys that is, at least in some ways, similar to human handedness.

Whether an individual is right- or left-handed has a number of interesting consequences. As will be obvious to left-handers, the world of human artifacts is in many respects a right-handed one (Figure A). Implements such as scissors, knives, coffee pots, and power tools are constructed for the right-handed majority. Books and magazines are also designed for right-handers (compare turning this page with your left and right hands), as are golf clubs and guitars. By the same token, the challenge of penmanship is different for left- and right-handers by virtue of writing from left to right (Figure B). Perhaps as a consequence of such biases, the accident rate for left-handers in all categories (work, home, sports) is higher than for right-handers, including the rate of traffic fatalities. However, there are also some advantages to being left-handed. For example, an inordinate number of international fencing champions have been left-handed. The reason for this fact is simply that the majority of any individual’s opponents will be right-handed; therefore, the average fencer, whether right- or left-handed, is less practiced at parrying thrusts from left-handers.

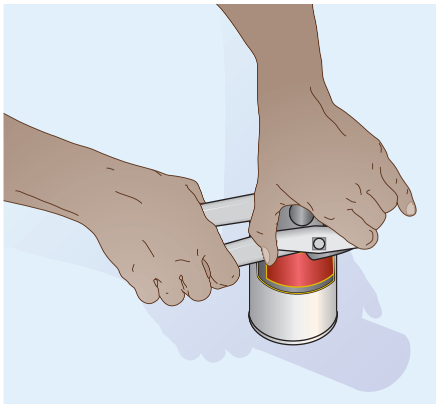
Hotly debated in recent years have been the related questions of whether being left-handed is in any sense “pathological,” and whether being left-handed entails a diminished life expectancy. No one disputes the fact that there is currently a surprisingly small number of left-handers among the elderly (Figure C). These data have come from studies of the

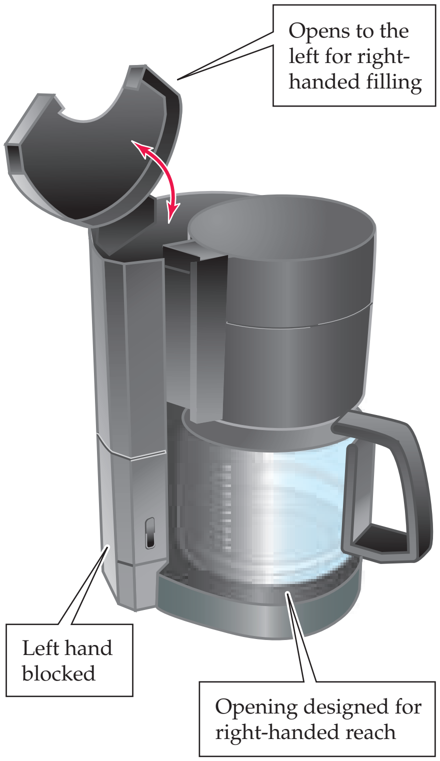
(A)

Right-handed

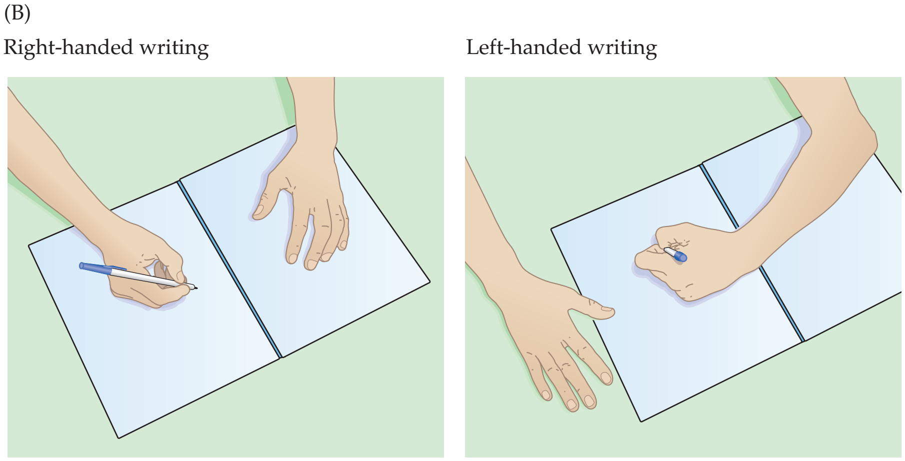


Left-handed

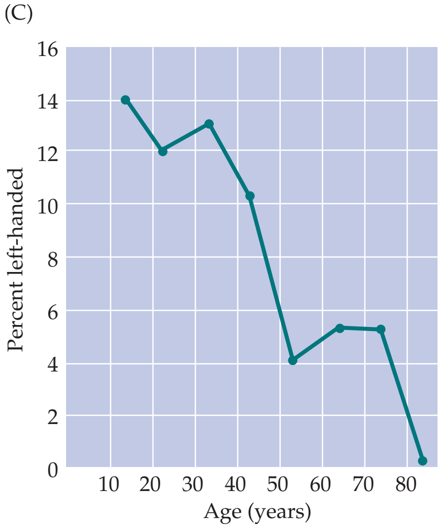



Opens to the left for right-handed filling
Left hand blocked
Opening designed for right-handed reach

Examples of common objects designed for use by the right-handed majority.



Writing techniques for right- and left-handed individuals.



The percentage of left-handers in the normal population as a function of age (based on more than 5000 individuals). Taken at face value, these data indicate that right-handers live longer than left-handers. Another possibility, however, is that the paucity of elderly left-handers at present may simply reflect changes over the decades in the social pressures on children to become right-handed. (From Coren, 1992.)

general population and have been supported by information gleaned from *The Baseball Encyclopedia* (in which longevity and other characteristics of a large number of healthy left- and right-handers have been recorded because of interest in the U.S. national pastime).

Two explanations of this peculiar finding have been put forward. Stanley Coren and his collaborators at the University of British Columbia have argued that these statistics reflect a higher mortality rate among left-handers partly as a result of increased accidents, but also because of other data that show left-handedness to be associated with a variety of pathologies (there is, for instance, a higher incidence of left-handedness among individuals classified as mentally retarded). Coren and others have suggested that left-handedness may arise because of developmental problems in the pre- and/or perinatal period. If true, then a rationale for decreased longevity would have been identified that might combine with greater proclivity to accidents in a right-hander's world.

An alternative explanation, however, is that the diminished number of left-handers among the elderly is primarily a reflection of sociological factors—namely, a greater acceptance of left-handed children today compared to the first half of the twentieth century. In this view, there are fewer older left-handers now because in earlier generations parents, teachers, and other authority figures encouraged (and sometimes insisted on) right-handedness. The weight of the evidence favors the sociological explanation.

The relationship between handedness and other lateralized functions—language in particular—has long been a source of confusion. It is unlikely that there is any direct relationship between language and handedness, despite much speculation to the contrary. The most straightforward evidence on this point comes from the results of the Wada test described in the text. The large number of such tests carried out for clinical purposes indicate that about 97% of humans, including the majority of left-handers, have their major language functions in the left hemisphere (although it should be noted that right hemispheric dominance for language is much more common among left-handers). Since most left-handers have language function on the side of the brain opposite the control of their preferred hand, it is hard to argue for any strict relationship between these two lateralized functions. In all likelihood, handedness, like language, is first and foremost an example of the advantage of having any specialized function on one side of the brain or the other to make maximum use of the available neural circuitry in a brain of limited size.

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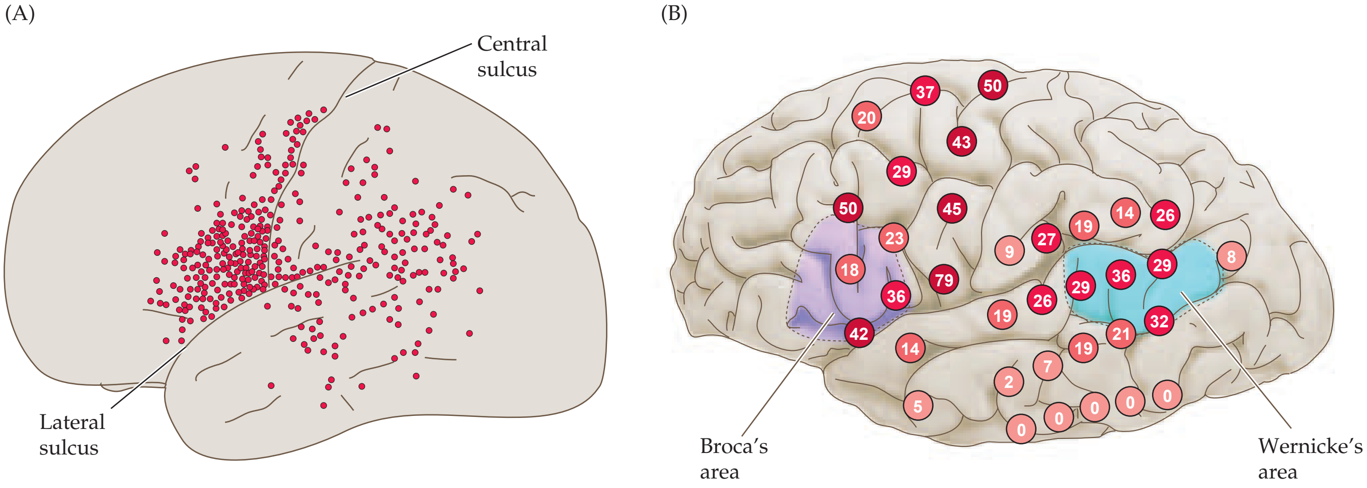
Less invasive (but less definitive) ways to test the cognitive abilities of the two hemispheres in normal subjects include positron emission tomography, functional magnetic resonance imaging (see Box C in Chapter 1), and the sort of tachistoscopic presentation used so effectively by Sperry and his colleagues (even when the hemispheres are normally connected, subjects show delayed verbal responses and other differences when the right hemisphere receives the instruction). Application of these various techniques, together with noninvasive brain imaging, has amply confirmed the hemispheric lateralization of language functions. More importantly, such studies have provided valuable diagnostic tools to determine, in preparation for neurosurgery, which hemisphere is "eloquent": although most individuals have the major language functions in the left hemisphere, a few—about 3% of the population—do not (the latter are much more often left-handed; see Box D).

Once the appropriate hemisphere is known by these means, neurosurgeons typically map language functions more precisely by electrical stimulation of the cortex during the surgery to further refine their approach to the problem at hand. By the 1930s, the neurosurgeon Wilder Penfield and his colleagues at the Montreal Neurological Institute had already carried out a detailed localization of cortical capacities in a large number of patients (see Chapter 8). Penfield used electrical mapping techniques adapted from neurophysiological work in animals to delineate the language areas of the cortex prior to removing brain tissue in the treatment of tumors or epilepsy. Such intraoperative mapping guaranteed that the cure would not be worse than the disease and has been widely used ever since, with increasingly sophisticated stimulation and recording methods. As a result, a wealth of more detailed information about language localization has emerged.

Penfield's observations, together with more recent studies performed by George Ojemann and his group at the University of Washington, have further advanced the conclusions inferred from postmortem correlations and other approaches. As expected, intraoperative studies using electrophysiological recording methods have shown that a large region of the perisylvian cortex of the left hemisphere is clearly involved in language production and comprehension (Figure 26.5). A surprise, however, has been the variability in language localization from patient to patient. Ojemann found that the brain regions involved in language are only approximately those indicated by older textbook treatments, and that their exact locations differ unpredictably among individuals. Equally unexpected, bilingual patients do not necessar-

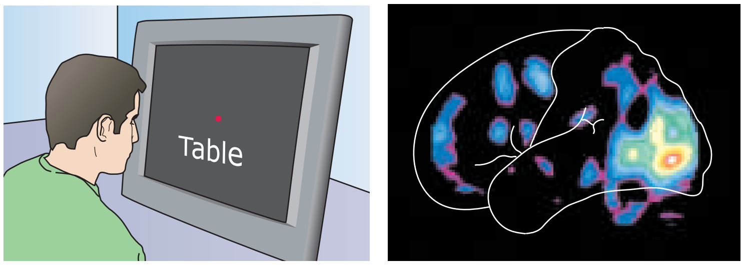
Figure 26.5 Evidence for the variability of language representation among individuals, determined by electrical stimulation during neurosurgery. (A) Diagram from Penfield's original study illustrating sites in the left hemisphere at which electrical stimulation interfered with speech. (B) Diagrams summarizing data from 117 patients whose language areas were mapped by electrical recording at the time of surgery. The number in each red circle indicates the (quite variable) percentage of patients who showed interference with language in response to stimulation at that site. Note also that many of the sites that elicited interference fall outside the classic language areas (Broca's area, shown in purple; Wernicke's area, shown in blue). (A after Penfield and Roberts, 1959; B after Ojemann et al., 1989.)



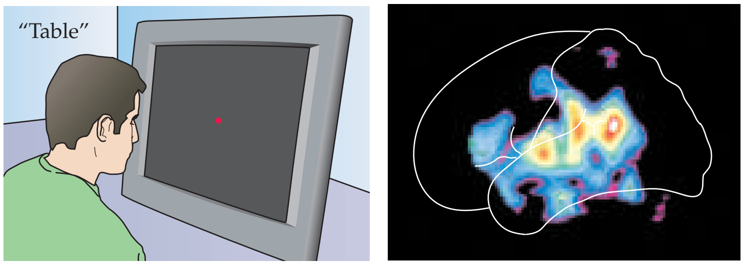
ily use the same bit of cortex for storing the names of the same objects in two different languages. Moreover, although single neurons in the temporal cortex in and around Wernicke's area respond preferentially to spoken words, they do not show preferences for a particular word. Rather, a wide range of words can elicit a response in any given neuron.

Despite these advances, neurosurgical studies are complicated by their intrinsic difficulty and to some extent by the fact that the brains of the patients in whom they are carried out are not normal. The advent of positron emission tomography in the 1980s, and more recently functional magnetic resonance imaging, has allowed the investigation of the language regions in normal subjects by noninvasive brain imaging (Figure 26.6). Recall that these

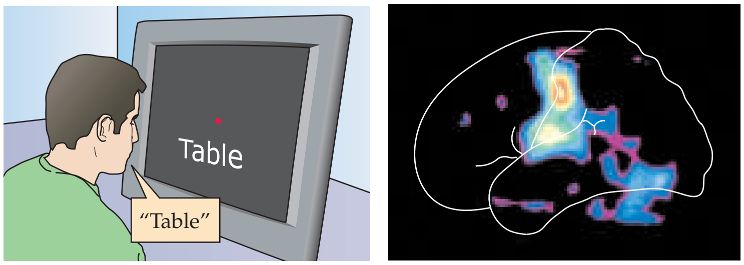
Passively viewing words



Listening to words



Speaking words



Generating word associations

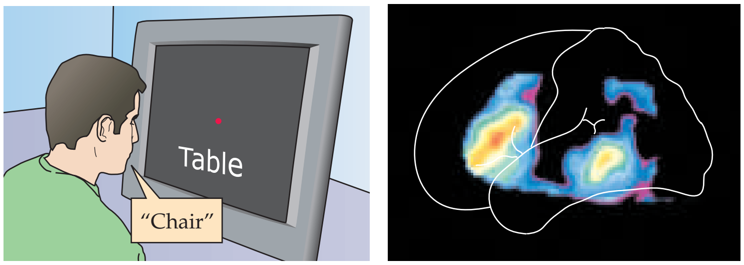


Figure 26.6 Language-related regions of the left hemisphere mapped by positron emission tomography (PET) in a normal human subject. Subjects reclined within the PET scanner and followed instructions on a special display (these details are not illustrated). The left panels indicate the task being practiced prior to scanning. The PET scan images are shown on the right. Language tasks such as listening to words and generating word associations elicit activity in Broca's and Wernicke's areas, as expected. However, there is also activity in primary and association sensory and motor areas for both active and passive language tasks. These observations indicate that language processing involves cortical regions in addition to the classic language areas. (From Posner and Raichle, 1994.)

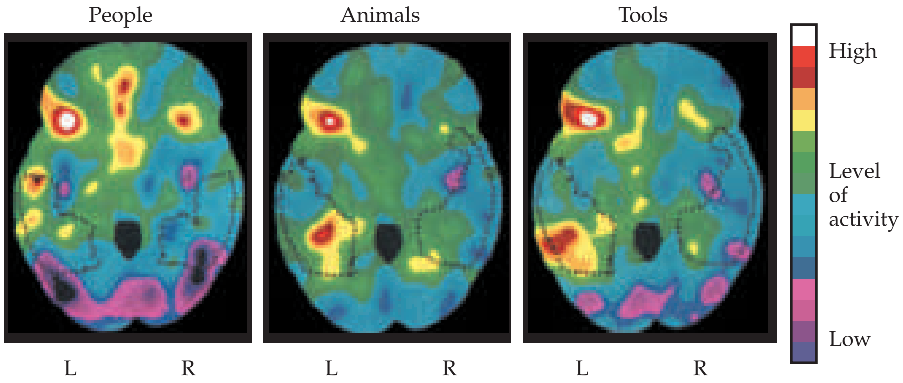


Figure 26.7 Different regions in the temporal lobe are activated by different word categories using PET imaging. Dotted lines show location of the relevant temporal regions in these horizontal views. Note the different patterns of activity in the temporal lobe in response to each stimulus catagory. (After Damasio et al., 1996.)

techniques reveal the areas of the brain that are active during a particular task because the related electrical activity increases local metabolic activity and therefore local blood flow (see Boxes B and C in Chapter 1). Much like Ojemann's studies in neurosurgical patients, the results of this approach, particularly in the hands of Marc Raichle, Steve Petersen, and their colleagues at Washington University in St. Louis, have challenged excessively rigid views of the localization and lateralization of linguistic function. Although high levels of activity occur in the expected regions, large areas of both hemispheres are activated in word recognition or production tasks.

Finally, Hanna Damasio and her colleagues at the University of Iowa have shown that distinct regions of the temporal cortex are activated by tasks in which subjects named particular people, animals, or tools (Figure 26.7). This arrangement helps explain the clinical finding that when a relatively limited region of the temporal lobe is damaged (usually by a stroke on the left side), language deficits are sometimes restricted to a particular category of objects. These studies are also consistent with Ojemann's electrophysiological studies, indicating that language is apparently organized according to categories of meaning rather than individual words. Taken together, such studies are rapidly augmenting the information available about how language is represented in the brain.

The Role of the Right Hemisphere in Language

Because exactly the same cytoarchitectonic areas exist in the cortex of both hemispheres, a puzzling issue remains. What do the comparable areas in the right hemisphere actually do? In fact, language deficits often *do* occur following damage to the right hemisphere. The most obvious effect of such lesions is an absence of the normal emotional and tonal components of language—called **prosodic elements**—that impart additional meaning to verbal communication. This "coloring" of speech is critical to the message conveyed, and in some languages (e.g., Mandarin Chinese) is even used to change the literal meaning of the word uttered. These deficiencies, referred to as **aprosodias**, are associated with right-hemisphere damage to the cortical regions that correspond to Broca's and Wernicke's areas and associated regions in the left hemisphere. The aprosodias emphasize that although the left hemisphere (or, better put, distinct cortical regions within that hemisphere) figures prominently in the comprehension and production of language for most humans, other regions, including areas in the right hemisphere, are needed to generate the full richness of everyday speech.

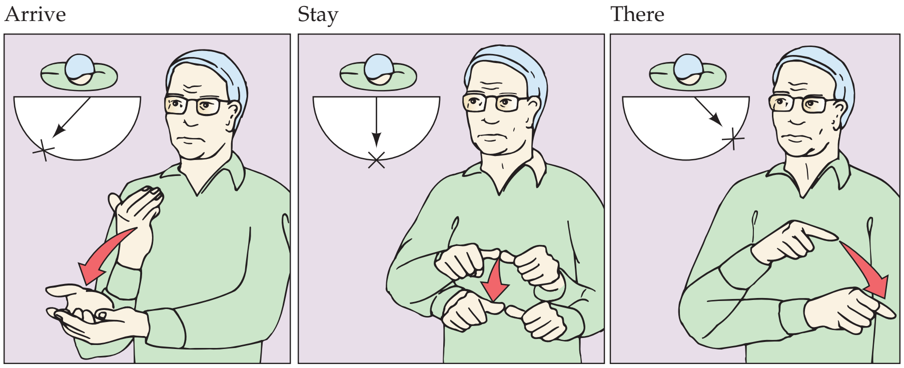
In summary, whereas the classically defined regions of the left hemisphere operate more or less as advertised, a variety of more recent studies have shown that other left- and right-hemisphere areas clearly make a significant contribution to generation and comprehension of language.

Sign Language

The implication of at least some aspects of the foregoing account is that the cortical organization of language does not simply reflect specializations for hearing and speaking; the language regions of the brain appear to be more broadly organized for processing symbols pertinent to social communication. Strong support for this conclusion has come from studies of sign language in individuals deaf from birth.

American Sign Language has all the components (e.g., grammar, syntax, and emotional tone) of spoken and heard language. Based on this knowledge, Ursula Bellugi and her colleagues at the Salk Institute examined the cortical localization of sign language abilities in patients who had suffered lesions of either the left or right hemisphere. All these deaf individuals never learned language, had been signing throughout their lives, had deaf spouses, were members of the deaf community, and were right-handed. The patients with left-hemisphere lesions, which in each case involved the language areas of the frontal and/or temporal lobes, had measurable deficits in sign production and comprehension when compared to normal signers of similar age (Figure 26.8). In contrast, the patients with lesions in approxi-

Patient with signing deficit:



Correct form:

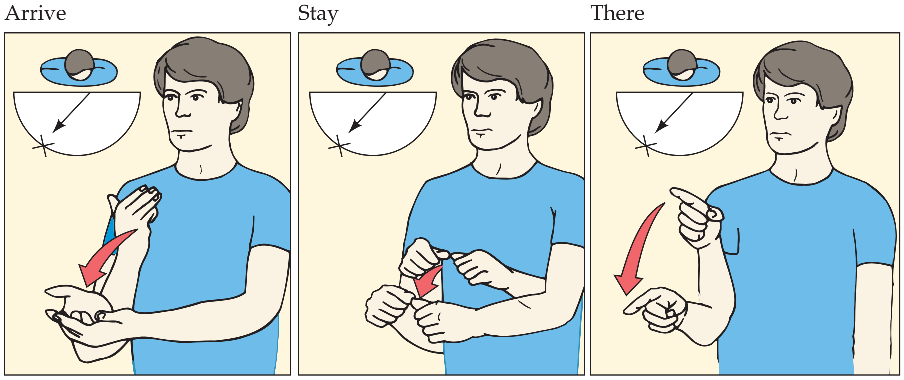


Figure 26.8 Signing deficits in congenitally deaf individuals who had learned sign language from birth and later suffered lesions of the language areas in the left hemisphere. Left hemisphere damage produced signing problems in these patients analogous to the aphasias seen after comparable lesions in hearing, speaking patients. In this example, the patient (upper panels) is expressing the sentence "We arrived in Jerusalem and stayed there." Compared to a normal control (lower panels), he cannot properly control the spatial orientation of the signs. The direction of the correct signs and the aberrant direction of the "aphasic" signs are indicated in the upper left-hand corner of each panel. (After Bellugi et al., 1989.)

mately the same areas in the right hemisphere did not have signing "aphasias." Instead, as predicted from other hearing patients with similar lesions, right hemisphere abilities such as visuospatial processing, emotional processing and the emotional tone evident in signing were impaired. Although the number of subjects studied was necessarily small (deaf signers with lesions of the language areas are understandably difficult to find), the capacity for signed and seen communication is evidently represented predominantly in the left hemisphere, in the same areas as spoken language. This evidence accords with the idea that the language regions of the brain are specialized for the representation of social communication by means of symbols, rather than for heard and spoken language per se.

The capacity for seen and signed communication, like its heard and spoken counterpart, emerges in early infancy. Careful observation of babbling in hearing (and, eventually, speaking) infants shows the production of a predictable pattern of sounds related to the ultimate acquisition of spoken language. Thus, babbling prefigures true language, and indicates that an innate capacity for language imitation is a key part of the process by which a full-blown language is ultimately acquired. The offspring of deaf, signing parents "babble" with their hands in gestures that are apparently the forerunners of signs (see Figure 23.1). Like verbal babbling, the amount of manual babbling increases with age until the child begins to form accurate, meaningful signs. These observations indicate that the strategy for acquiring the rudiments of symbolic communication from parental or other cues—regardless of the means of expression—is similar.

Summary

A variety of methods have all been used to understand the organization of language in the human brain. This effort began in the nineteenth century by correlating clinical signs and symptoms with the location of brain lesions determined postmortem. In the twentieth century, additional clinical observations together with studies of split-brain patients, mapping at neurosurgery, transient anesthesia of a single hemisphere, and noninvasive imaging techniques such as PET and *f*MRI have greatly extended knowledge about the neural substrates of language. Together, these various approaches show that the perisylvian cortices of the left hemisphere are especially important for normal language in the vast majority of humans. The right hemisphere also contributes importantly to language, most obviously by giving it emotional tone. The similarity of the deficits after comparable brain lesions in congenitally deaf individuals and their speaking counterparts have shown further that the cortical representation of language is independent of the means of its expression or perception (spoken and heard, versus gestured and seen). The specialized language areas that have been identified are evidently the major components of a widely distributed set of brain regions that allow humans to communicate effectively by means of symbols that can be attached to objects, concepts and feelings.

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Chapter 27

Sleep and Wakefulness

Overview

Sleep—which is defined behaviorally by the normal suspension of consciousness and electrophysiologically by specific brain wave criteria—consumes fully a third of our lives. Sleep occurs in all mammals, and probably in all vertebrates. We crave sleep when deprived of it and, to judge from some animal studies, continued sleep deprivation can ultimately be fatal. Surprisingly, however, this peculiar state is not the result of a simple diminution of brain activity; for example, in REM (rapid eye movement) sleep, the brain is about as active as it is when people are awake. Rather, sleep is a series of precisely controlled brain states, the sequence of which is governed by a group of brainstem nuclei that project widely throughout the brain and spinal cord. The reason for such high levels of brain activity during REM sleep, the significance of dreaming, and the basis of the restorative effect of sleep are all topics that remain poorly understood. The clinical importance of sleep is obvious from the prevalence of sleep disorders (insomnias). In any given year about 40 million Americans suffer from chronic sleep disorders, and an additional 30 million experience occasional (at least a few days each month) sleeping problems that are severe enough to interfere with their daily activities.

Why Do Humans (and Many Other Animals) Sleep?

To feel rested and refreshed upon awakening, most adults require 7–8 hours of sleep, although this number varies among individuals (Figure 27.1A). As a result, a substantial fraction of our lives is spent in this mysterious state. For infants, the requirement is much higher (17 hours a day or more), and teenagers need on average about 9 hours of sleep. As people age, they tend to sleep more lightly and for shorter times at night, although their need for sleep is probably not much less than in early adulthood (Figure 27.1B). Thus, older adults often "make up" for shorter and lighter nightly sleep periods by napping during the day. Getting too little sleep creates a "sleep debt" that must be repaid in the following days. In the meantime, judgment, reaction time, and other functions are in varying degrees impaired. Poor sleep therefore has a price, sometimes with tragic consequences. In the United States alone, fatigue is estimated to contribute to more than 100,000 highway accidents each year, resulting in some 70,000 injuries and 1,500 deaths.

Sleep (or at least a physiological period of quiescence) is a highly conserved behavior that occurs in animals ranging from fruit flies to humans (Box A). Despite this prevalence, *why* we sleep is not well understood. Since an animal is particularly vulnerable while sleeping, there must be evolutionary advantages that outweigh this considerable disadvantage. Shakespeare

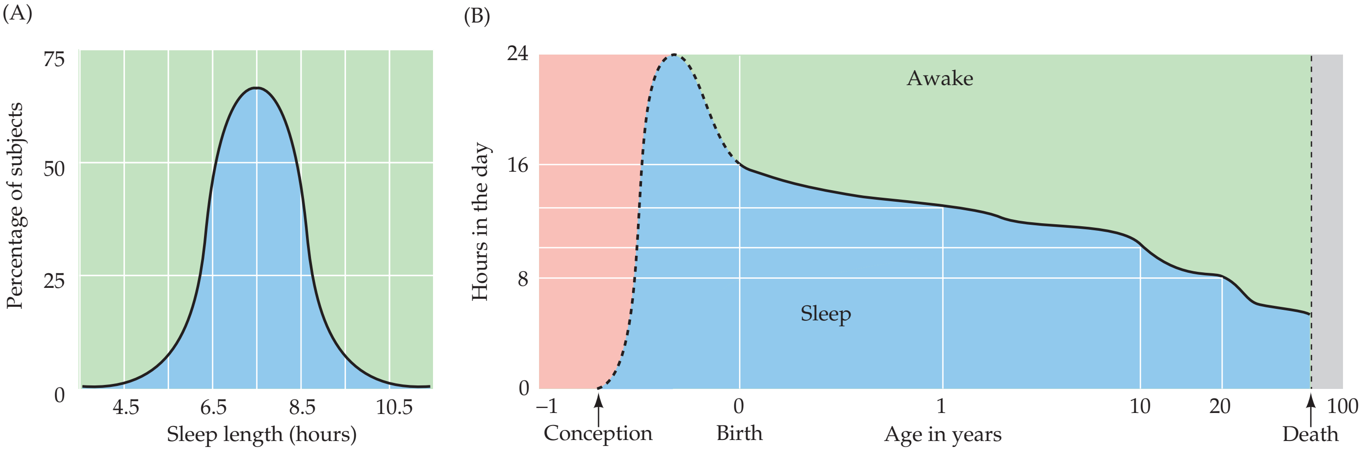

Figure 27.1 The duration of sleep. (A) The duration of sleep each night in adults is normally distributed with a mean of 7.5 hours and a standard deviation of about 1.25 hours. Thus, each night about two-thirds of the population sleeps between 6.25 and 8.75 hours. (B) The duration of daily sleep as a function of age. (After Hobson, 1989.)

called sleep "nature's soft nurse," emphasizing (as have many others) the restorative nature of sleep. From a perspective of energy conservation, one function of sleep is to replenish brain glycogen levels, which fall during the waking hours. In addition, since it is generally colder at night, more energy would have to be expended to keep warm were we nocturnally active. Body temperature has a 24-hour cycle (as do many other indices of activity and stress), reaching a minimum at night and thus reducing heat loss (Figure 27.2). As might be expected, metabolism measured by oxygen consumption decreases during sleep. Another plaausible reason is that humans and many other animals that sleep at night are highly dependent on visual information to find food and avoid predators.

Whatever the reasons for sleeping, in mammals sleep is evidently necessary for survival. Sleep-deprived rats lose weight despite increasing food intake and progressively fail to regulate body temperature as their core temperature increases several degrees. They also develop infections, suggesting some compromise of the immune system. Rats completely deprived of sleep

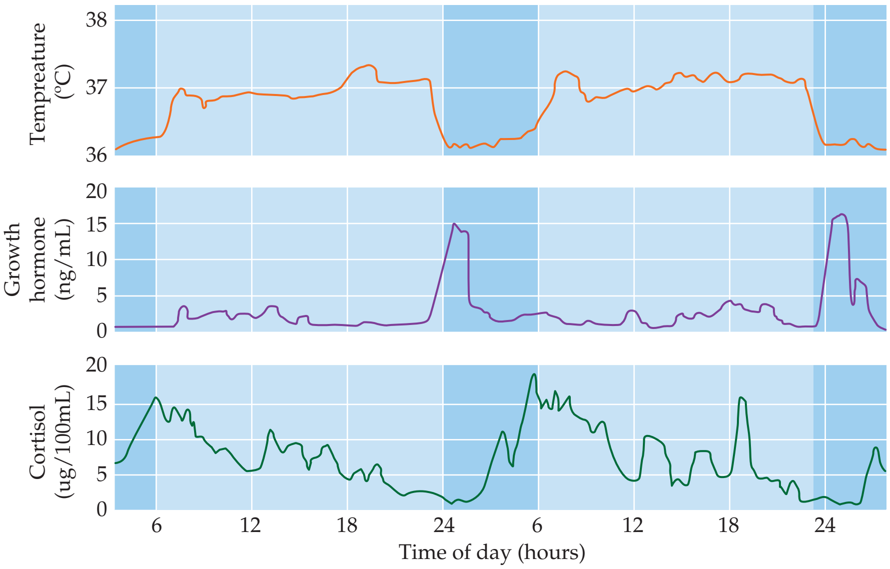

Figure 27.2 Circadian rhythmicity of core body temperature, and of growth hormone and cortisol levels in the blood. In the early evening, core temperature begins to decrease whereas growth hormone begins to increase. The level of cortisol, which reflects stress, begins to increase in the morning and stays elevated for several hours.

Box A

Styles of Sleep in Different Species

A wide variety of animals have a rest–activity cycle that often (but not always) occurs in a daily (circadian) rhythm. Even among mammals, however, the organization of sleep depends very much on the species in question. As a general rule, predatory animals can indulge, as humans do, in long, uninterrupted periods of sleep that can be nocturnal or diurnal, depending on the time of day when the animal acquires food, mates, cares for its young, and deals with life's other necessities. The survival of animals that are preyed upon, however, depends much more critically on continued vigilance. Such species—as diverse as rabbits and giraffes—sleep during short intervals that usually last no more than a few minutes. Shrews, the smallest mammals, hardly sleep at all.

An especially remarkable solution to the problem of maintaining vigilance during sleep is shown by dolphins and seals, in whom sleep alternates between the two cerebral hemispheres (see figure). Thus, one hemisphere can exhibit the electroencephalographic signs of wakefulness, while the other shows the characteristics of sleep (see Box C and Figure 27.5). In short, although periods of rest are evidently essential to the proper functioning of the brain, and more generally to normal homeostasis, the manner in which rest is obtained depends on the particular needs of each species.

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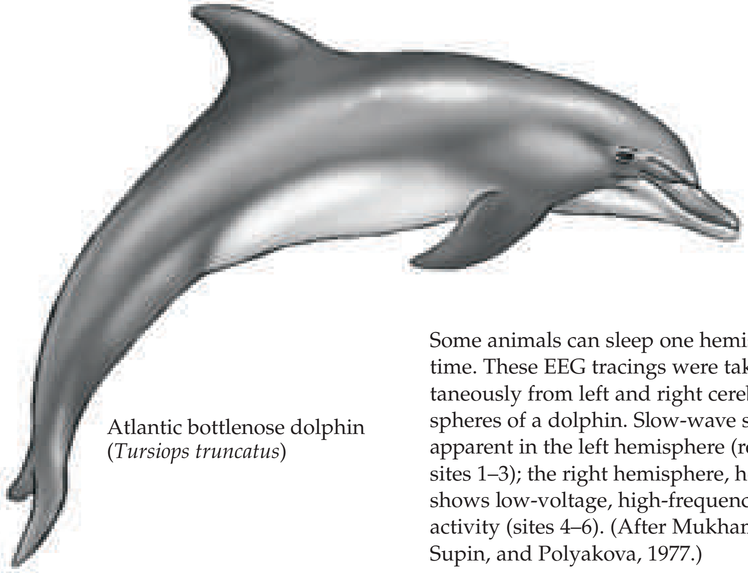
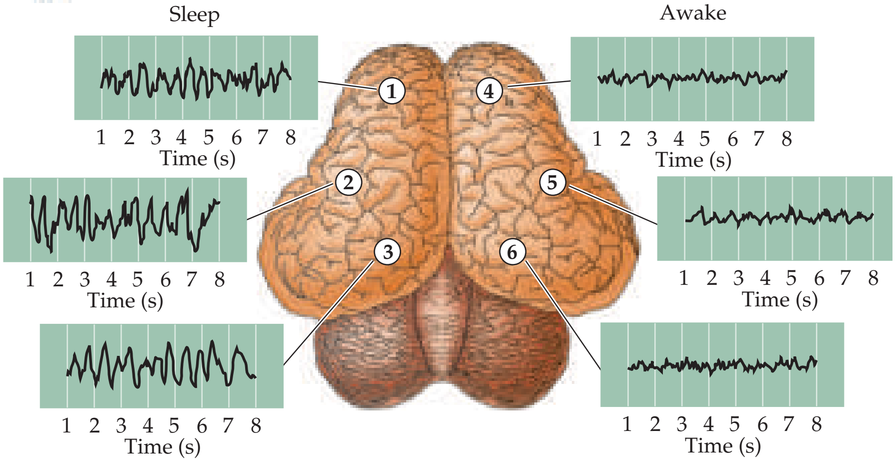


Atlantic bottlenose dolphin (*Tursiops truncatus*)

Some animals can sleep one hemisphere at a time. These EEG tracings were taken simultaneously from left and right cerebral hemispheres of a dolphin. Slow-wave sleep is apparent in the left hemisphere (recording sites 1–3); the right hemisphere, however, shows low-voltage, high-frequency waking activity (sites 4–6). (After Mukhametov, Supin, and Polyakova, 1977.)



die within a few weeks (Figure 27.3A,B). In humans, lack of sleep leads to impaired memory and reduced cognitive abilities and, if the deprivation persists, mood swings and often hallucinations. Patients with the genetic disease *fatal familial insomnia*—as the name implies—die within several years of onset. This disease, which appears in middle age, is characterized by hallucinations, seizures, loss of motor control, and the inability to enter a state of deep sleep (see the section "Stages of Sleep").

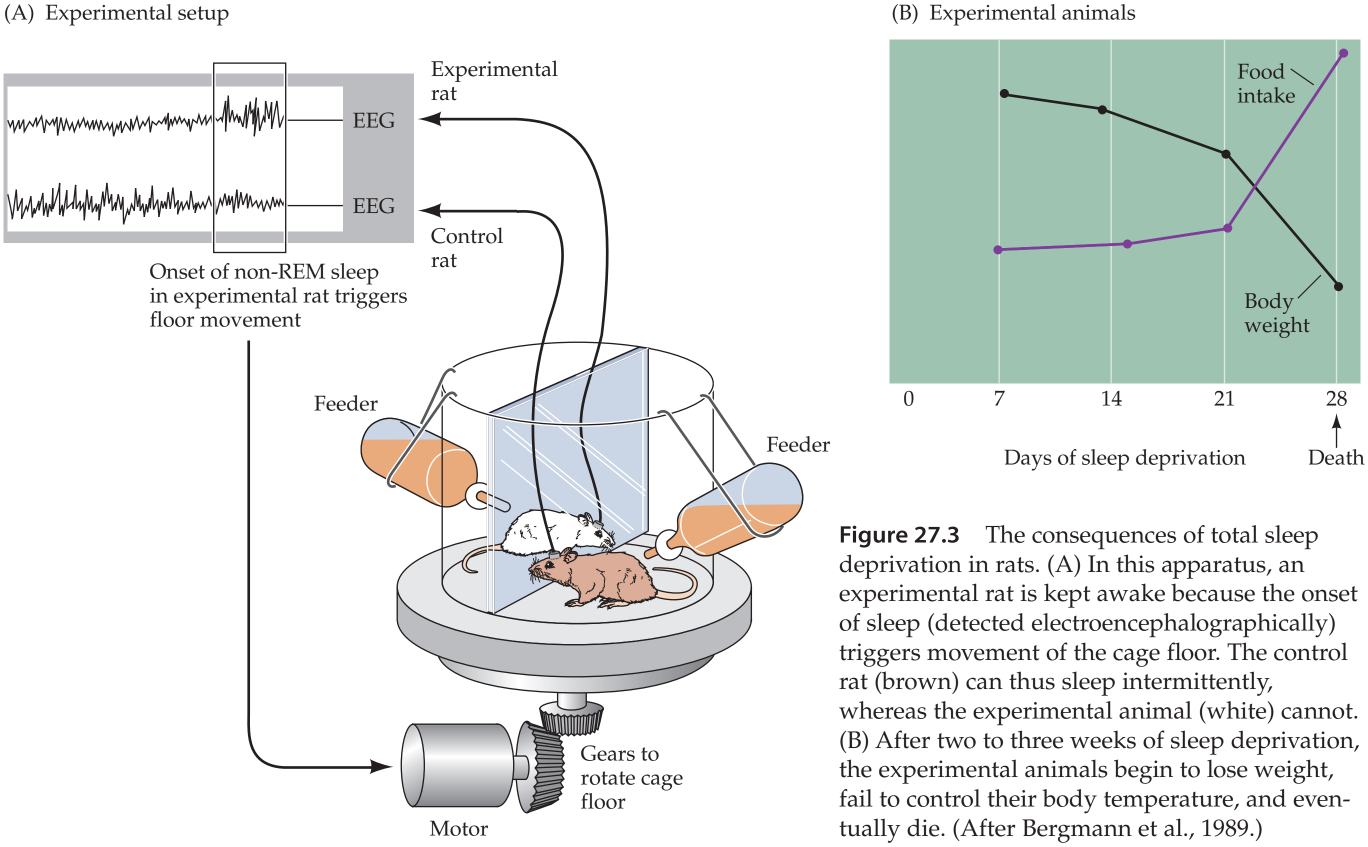

(A) Experimental setup
EEG
EEG
Experimental rat
Control rat
Onset of non-REM sleep in experimental rat triggers floor movement
Feeder
Feeder
Gears to rotate cage floor
Motor
(B) Experimental animals
Food intake
Body weight
0
7
14
21
28
Days of sleep deprivation
Death

Figure 27.3 The consequences of total sleep deprivation in rats. (A) In this apparatus, an experimental rat is kept awake because the onset of sleep (detected electroencephalographically) triggers movement of the cage floor. The control rat (brown) can thus sleep intermittently, whereas the experimental animal (white) cannot. (B) After two to three weeks of sleep deprivation, the experimental animals begin to lose weight, fail to control their body temperature, and eventually die. (After Bergmann et al., 1989.)

The longest documented period of voluntary sleeplessness in humans is 453 hours, 40 minutes (approximately 19 days)—a record achieved without any pharmacological stimulation. The young man involved recovered after a few days, during which he slept more than normal, but otherwise seemed none the worse for wear.

The Circadian Cycle of Sleep and Wakefulness

Human sleep occurs with circadian (*circa* = about; *dia* = day) periodicity, and biologists interested in circadian rhythms have explored a number of questions about this daily cycle. What happens, for example, when individuals are prevented from sensing the cues they normally use to distinguish night and day? This question has been addressed by placing volunteers in an environment such as a cave or bunker that lacks external time cues (Figure 27.4). In a typical experiment of this sort, subjects undergo a 5- to 8-day period that included social interactions, meals at normal times, and temporal cues (radio, TV). During this acclimation period, the subjects arose and went to sleep at the usual times and maintained a 24-hour sleep–wake cycle. After removing these normal cues, however, the subjects awakened later each day, and the cycle of sleep and wakefulness gradually lengthened to about 26 hours. When the volunteers returned to a normal environment, the 24-hour cycle was rapidly restored. Thus, humans (and many other animals; see Box B) have an internal "clock" that operates even in the absence of external information about the time of day; under these conditions, the clock is said to be "free-running."

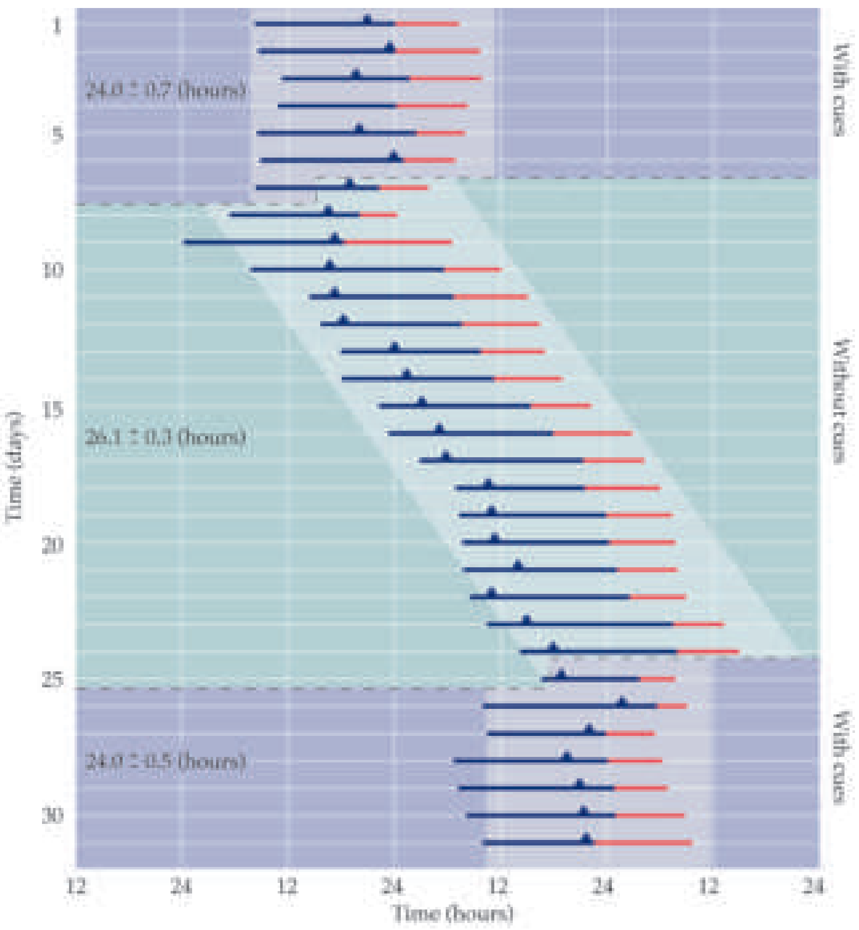


Figure 27.4 Rhythm of waking (blue lines) and sleeping (red lines) of a volunteer in an isolation chamber with and without cues about the day–night cycle. Numbers represent the mean ± standard deviation of a complete wake–sleep cycle in each condition. Triangles represent times when the rectal temperature was maximum. (After Aschoff, 1965, as reproduced in Schmidt et. al., 1983)

Presumably, circadian clocks evolved to maintain appropriate periods of sleep and wakefulness and to control other daily rhythms in spite of the variable amount of daylight and darkness in different seasons and at different places on the planet. To synchronize physiological processes with the day-night cycle (called *photoentrainment*), the biological clock must detect decreases in light levels as night approaches. The receptors that sense these light changes are, not surprisingly, in the outer nuclear layer of the retina, as demonstrated by the fact that removing or covering the eyes abolishes photoentrainment. The detectors are not, however, the rods or cones (Figure 27.5A). Rather, these cells lie within the ganglion cell layer of the primate and murine retinas. Unlike rods and cones that are hyperpolarized when activated by light (see Chapter 11), this special class of ganglion cells contains a novel photopigment called melanopsin and are depolarized by light. The function of these unusual photoreceptors is evidently to encode environmental illumination and to set the biological clock. This regulation is achieved via axons running the retinohypothalmic tract (Figure 27.5B), which projects to the **suprachiasmatic nucleus (SCN)** of the anterior hypothalamus, the site of the circadian control of homeostatic functions.

Activation of the SCN evokes responses in neurons whose axons first synapse in the paraventricular nucleus of the hypothalamus and descend to the preganglionic sympathetic neurons in intermediolateral zone in the lateral horns of the thoracic spinal cord. As described in Chapter 20, these pregan-

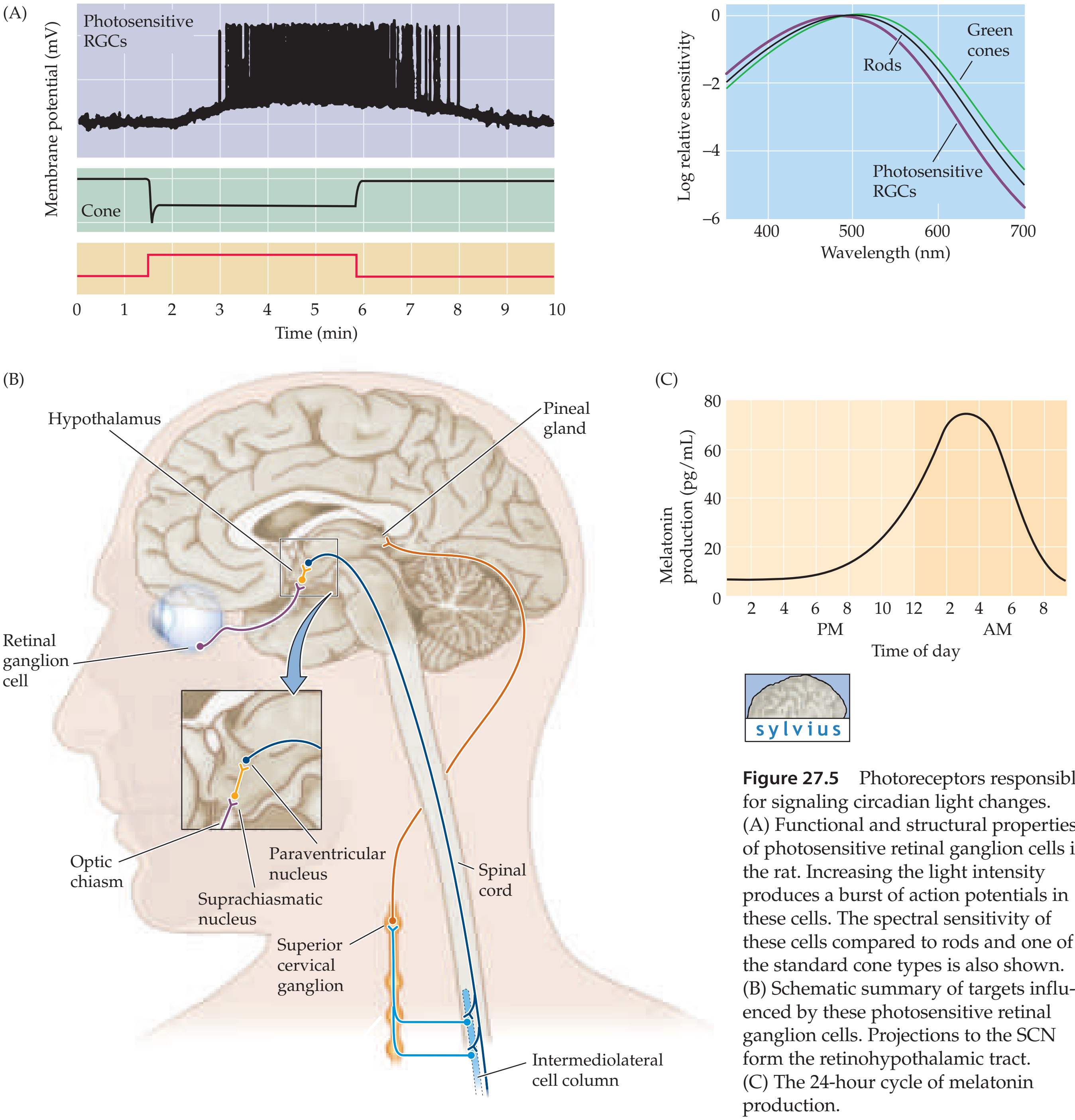


Figure 27.5 Photoreceptors responsible for signaling circadian light changes. (A) Functional and structural properties of photosensitive retinal ganglion cells in the rat. Increasing the light intensity produces a burst of action potentials in these cells. The spectral sensitivity of these cells compared to rods and one of the standard cone types is also shown. (B) Schematic summary of targets influenced by these photosensitive retinal ganglion cells. Projections to the SCN form the retinohypothalamic tract. (C) The 24-hour cycle of melatonin production.

glionic neurons modulate neurons in the superior cervical ganglia whose postganglionic axons project to the **pineal gland** (*pineal* means "pinecone-shaped") in the midline near the dorsal thalamus (Figure 27.5B). The pineal gland synthesizes the sleep-promoting neurohormone melatonin (*N*-acetyl-5-methoxytryptamine) from tryptophan, and secretes melatonin into the bloodstream where it modulates the brainstem circuits that ultimately govern the sleep–wake cycle. Melatonin synthesis increases as the light in the environment decreases and reaches a maximum between 2 A.M. and 4:00 A.M. (Figure 27.5C). In the elderly, the pineal gland produces less melatonin, perhaps explaining why older people sleep less at night and are more often afflicted with insomnia. Melatonin has been used to promote sleep in elderly insomniacs and to reduce disruption of the biological clocks that occurs with jet lag, but whether these therapies are really effective remains unclear.

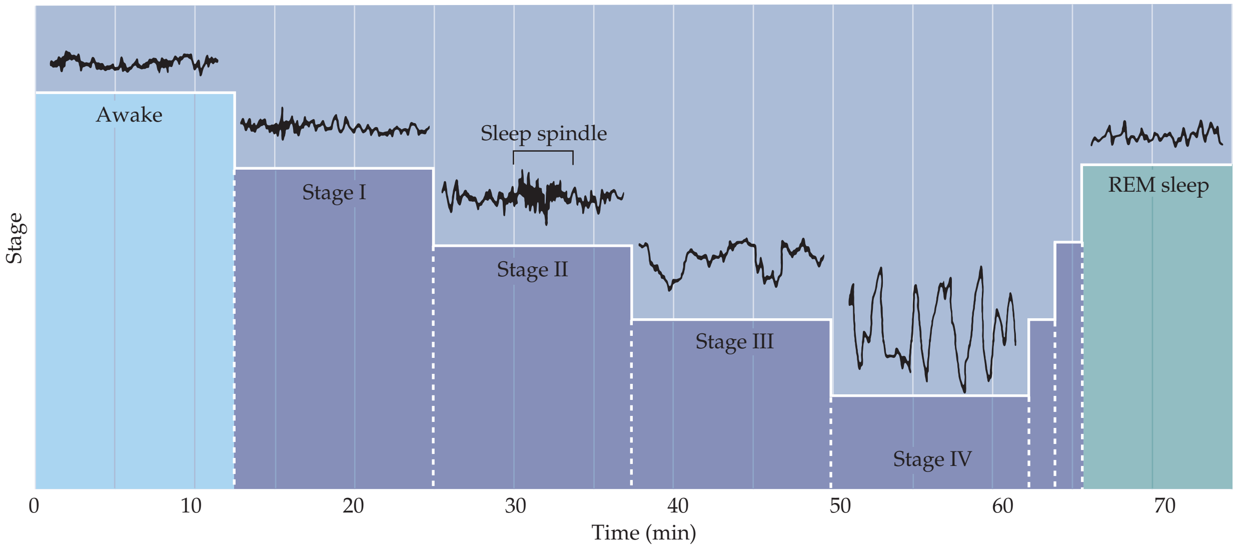
Most sleep researchers consider the superior chiasmatic nucleus to be the "master clock." Evidence for this conclusion is that its removal of the SCN in experimental animals abolishes their circadian rhythm of sleep and waking. Furthermore, when SCN cells are placed in organ culture, they exhibit characteristic circadian rhythms (Box B). The SCN also governs other functions that are synchronized with the sleep–wake cycle, including body temperature, hormone secretion (e.g., cortisol), blood pressure, and urine production (see Figure 27.2). In adults, urine production is reduced at night because of the circadian regulation of antidieuretic hormone (ADH or vasopressin) production. Some children and elderly individuals lack this circadian control (albeit for different reasons), as evidenced by bed-wetting.

Stages of Sleep

The normal cycle of human sleep and wakefulness implies that, at specific times, various neural systems are being activated while others are being turned off. For centuries—indeed up until the 1950s—most people who thought about sleep considered it a unitary phenomenon whose physiology was essentially passive and whose purpose was simply restorative. In 1953, however, Nathaniel Kleitman and Eugene Aserinksy showed, by means of electroencephalographic (EEG) recordings from normal subjects, that sleep actually comprises different stages that occur in a characteristic sequence.

Over the first hour after retiring, humans descend into successive stages of sleep (Figure 27.6). These characteristic stages are defined primarily by electroencephalographic (EEG) criteria (Box C). Initially, during "drowsi-

Figure 27.6 EEG recordings during the first hour of sleep. The waking state with the eyes open is characterized by high-frequency (15–60 Hz), low-amplitude activity (~30 μV) activity. This pattern is called beta activity. Descent into stage I non-REM sleep is characterized by decreasing EEG frequency (4–8 Hz) and increasing amplitude (50–100 μV), called theta waves. Descent into stage II non-REM sleep is characterized by 10–12 Hz oscillations (50–150 μV) called spindles, which occur periodically and last for a few seconds. Stage III non-REM sleep is characterized by slower waves at 2–4 Hz (100–150 μV). Stage IV sleep is defined by slow waves (also called delta waves) at 0.5–2 Hz (100–200 μV). After reaching this level of deep sleep, the sequence reverses and a period of rapid eye movement sleep, or REM sleep, ensues. REM sleep is characterized by low-voltage, high-frequency activity similar to the EEG activity of individuals who are awake. (Adapted from Hobson, 1989.)



Box B

Molecular Mechanisms of Biological Clocks

Virtually all plants and animals adjust their physiology and behavior to the 24-hour day–night cycle under the governance of circadian clocks. Molecular biological studies have now indicated much about the genes and proteins that make up the machinery of these clocks, a story that began about 30 years ago.

In the early 1970s, Ron Konopka and Seymour Benzer, working at the California Institute of Technology, discovered three mutant strains of fruit flies whose circadian rhythms were abnormal. Further analysis showed the mutants to be alleles of a single locus, which Konopka and Benzer called the *period* or *per* gene. In the absence of normal environmental cues (that is, in constant light or dark), wild-type flies have periods of activity geared to a 24-hour cycle; *per*^{s} mutants have 19 hour rhythms, *per*^{1} mutants have 29-hour rhythms, and *per*^{0} mutants have no apparent rhythm.

About 10 years later, Michael Young at Rockefeller University and Jeffrey Hall and Michael Rosbash at Brandeis University independently cloned the first of the three *per* genes. Cloning a gene does not necessarily reveal its function, however, and so it was in this case. Nonetheless, the gene product Per, a nuclear protein, is found in many *Drosophila* cells pertinent to the production of the fly's circadian rhythms. Moreover, normal flies show a circadian variation in the amount of *per* mRNA and Per protein, whereas *per*^{0} flies, which lack a circadian rhythm, do not show this circadian rhythmicity of gene expression.

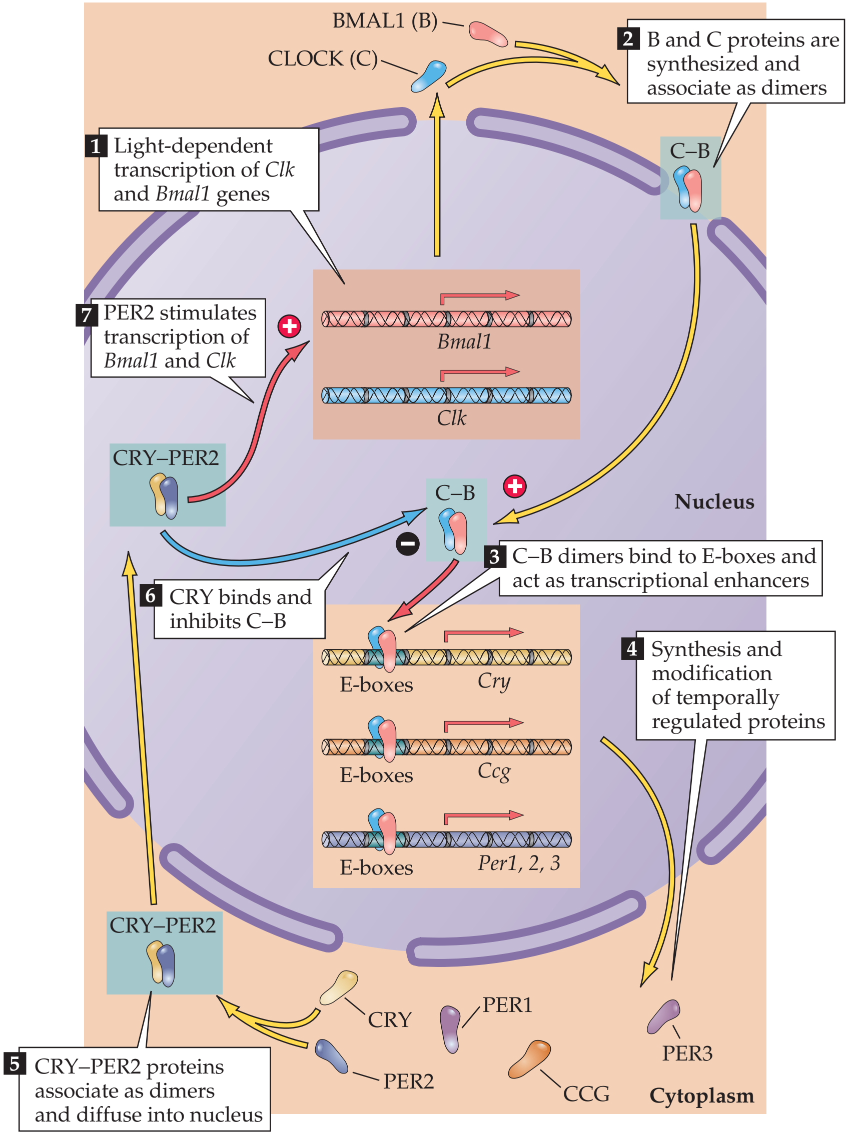

BMAL1 (B)
CLOCK (C)
2 B and C proteins are synthesized and associate as dimers
C–B
1 Light-dependent transcription of *Clk* and *Bmal1* genes
7 PER2 stimulates transcription of *Bmal1* and *Clk*
Bmal1
Clk
CRY–PER2
C–B
Nucleus
3 C–B dimers bind to E-boxes and act as transcriptional enhancers
6 CRY binds and inhibits C–B
E-boxes
Cry
4 Synthesis and modification of temporally regulated proteins
E-boxes
Ccg
E-boxes
Per1, 2, 3
CRY–PER2
CRY
PER1
PER3
5 CRY–PER2 proteins associate as dimers and diffuse into nucleus
PER2
CCG
Cytoplasm

Diagram illustrating molecular feedback loop that governs circadian clocks. (After Okamura et al., 1999.)

ness," the frequency spectrum of the electroencephalogram is shifted toward lower values and the amplitude of the cortical waves increases slightly. This drowsy period, called **stage I sleep**, eventually gives way to light or **stage II sleep**, which is characterized by a further decrease in the frequency of the EEG waves and an increase in their amplitude, together with intermittent

Many of the genes and proteins responsible for circadian rhythms in fruit flies have now been discovered in mammals. In mice, the circadian clock arises from the temporally regulated activity of proteins (in capital letters) and genes (in italics), including CRY (*cryptochrome*), CLOCK (C) (*Circadian locomotor output cycles kaput*), BMAL1 (B) (*brain and muscle, ARNT-like*), PER1 (*Period1*), PER2 (*Period2*), PER3 (*Period3*), and vasopressin prepropressophysin (VP) (*clock-controlled genes; ccg*). These genes and their proteins give rise to transcription/translation autoregulatory feedback loops with both excitatory and inhibitory components (see figure). The key points to understanding this system are: (1) that the concentrations of BMAL1 (B) and the three PER proteins cycle in counterpoint; (2) that PER2 is a positive regulator of the Bmal1 loop; and (3) that CRY is a negative regulator of the period and cryptochrome loops. The two positive components of this loop are influenced, albeit indirectly, by light or temperature.

At the start of the day, the transcription of Clk and Bmal1 commencences, and the proteins CLOCK (C) and BMAL1 (B) are synthesized in tandem. When the concentrations of C and B increase sufficiently, they associate as dimers and bind to regulatory DNA sequences (E-boxes) that act as a circadian transcriptional enhancers of the genes *Cry*, *Per1*, *Per2*, *Per3*, and *CCG*. As a result, the proteins PER1, 2, and 3, CRY, and proteins such as VP are produced. These proteins then diffuse from the nucleus into the cytoplasm, where they are modified.

Although the functions of PER1 and PER3 remain to be elucidated, when the cytoplasmic concentrations of PER2 and CRY increase, they associate as CRY–PER2, and diffuse back into the nucleus. Here, PER2 stimulates the synthesis of C, and B, and CRY binds to C–B dimers, inhibiting their ability to stimulate the synthesis of the other genes. The complete time course of these feedback loops is 24 hours.

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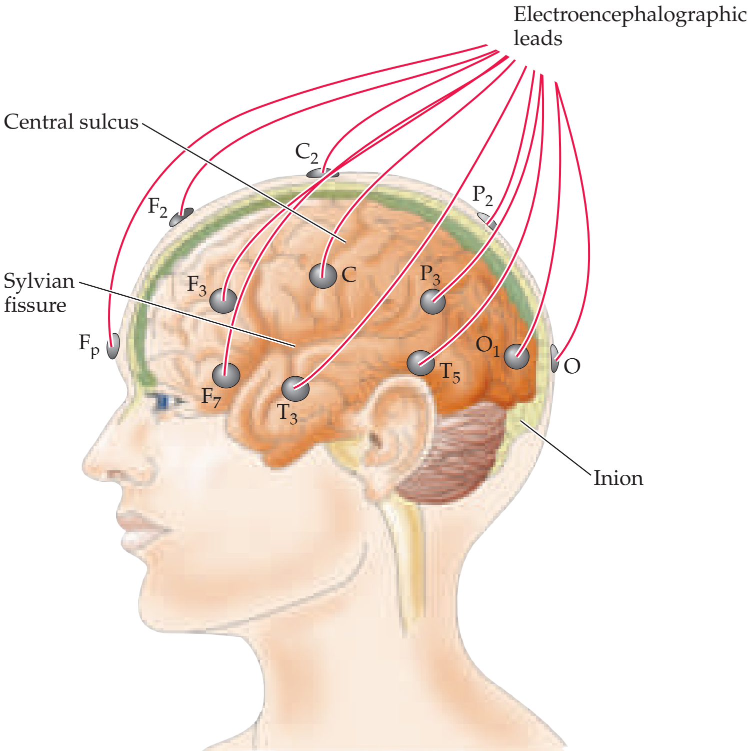
high-frequency spike clusters called **sleep spindles**. Sleep spindles are periodic bursts of activity at about 10–12 Hz that generally last 1–2 seconds and arise as a result of interactions between thalamic and cortical neurons. In **stage III sleep**, which represents moderate to deep sleep, the number of spindles decreases, whereas the amplitude of the EEG activity increases further and the frequency continues to fall. In the deepest level of sleep, **stage IV sleep**, also known as **slow-wave sleep,** the predominant EEG activity consists of very low frequency (0.5–2 Hz), high-amplitude fluctuations called **delta waves**, the characteristic slow waves for which this phase of sleep is named. (Note that these can also be thought of as reflecting synchronized electrical activity of cortical neurons.) The entire sequence from drowsiness to deep stage IV sleep usually takes about an hour.

These four sleep stages are called **non-rapid eye movement (non-REM) sleep**, and its most prominent feature is slow-wave (stage IV) sleep. It is more difficult to awaken people from slow-wave sleep, which is therefore considered to be the deepest stage of sleep. Following a period of slow-wave sleep, however, EEG recordings show that the stages of sleep reverse, entering a quite different state called **rapid eye movement** (**REM) sleep**. In REM sleep, EEG recordings are remarkably similar to those of the awake state (see Figure 27.6). After about 10 minutes in REM sleep, the brain typically cycles back through the non-REM sleep stages. Slow-wave sleep usually occurs

Box C
Electroencephalography

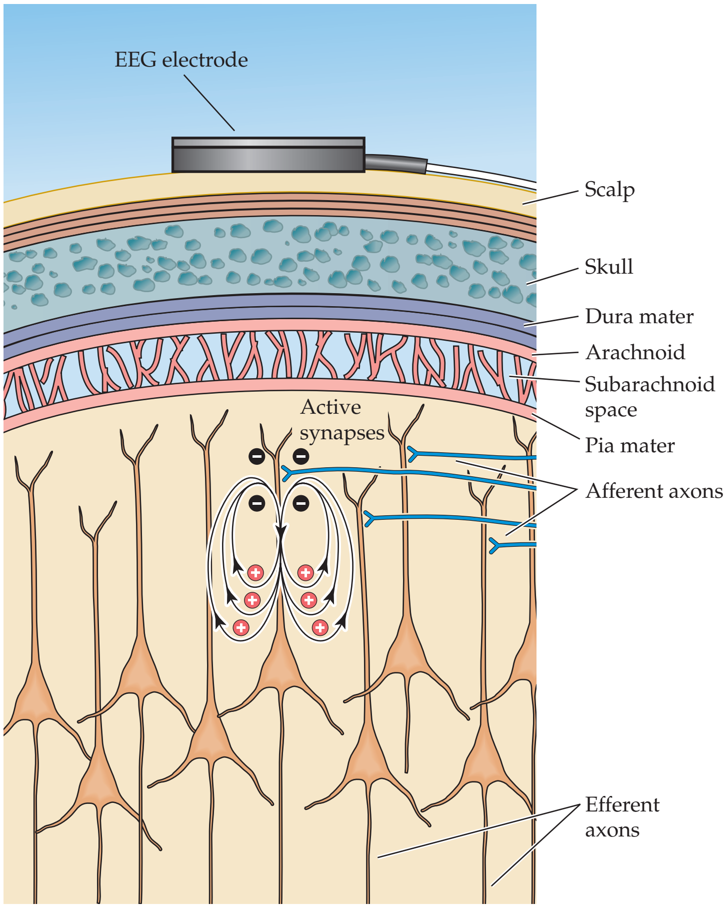
Although electrical activity recorded from the exposed cerebral cortex of a monkey was reported in 1875, it was not until 1929 that Hans Berger, a psychiatrist at the University of Jena, first made scalp recordings of this activity in humans. Since then, the electroencephalogram, or EEG, has received mixed press, touted by some as a unique opportunity to understand human thinking and denigrated by others as too complex and poorly resolved to allow anything more than a superficial glimpse of what the brain is actually doing. The truth lies somewhere in between. Certainly no one disputes that electroencephalography has provided a valuable tool to both researchers and clinicians, particularly in the fields of sleep physiology and epilepsy.



(A) The electroencephalogram represents the voltage recorded between two electrodes applied to the scalp. Typically, pairs of electrodes are placed in 19 standard positions distributed over the head. Letters indicate position (F = frontal, P = parietal, T = temporal, O = occipital, C = central). The recording obtained from each pair of electrodes is somewhat different because each samples the activity of a population of neurons in a different brain region.

The major advantage of electroencephalography, which involves the application of a set of electrodes to standard positions on the scalp (Figure A), is its great simplicity. Its most serious limitation is poor spatial resolution, allowing localization of an active site only to within several centimeters. Four basic EEG phenomena have been defined in humans (albeit somewhat arbitrarily). The alpha rhythm is typically recorded in awake subjects with their eyes closed. By definition, the frequency of the alpha rhythm is 8–13 Hz, with an amplitude that is typically 10–50 mV. Lower-amplitude beta activity is defined by frequencies of 14–60 Hz and is indicative of mental activity and attention. The theta and delta waves, which are characterized by frequencies of 4–7 Hz and less than 4 Hz, respectively, imply drowsiness, sleep, or one of a variety of pathological conditions; these slow waves in normal individuals are the signature of stage IV non-REM sleep. The way these phenomena are generated is indicated in Figures B and C.

Far and away the most obvious component of these various oscillations is the alpha rhythm. Its prominence in the occipital region—and its modulation by eye opening and closing—implies that it is somehow linked to visual processing, as was first pointed out in 1935 by the British physiologist E. D. Adrian. In fact, evidence from very large numbers of subjects suggests that at least several different regions of the brain have their own characteristic rhythms; for example, within the alpha band (8–13 Hz), one rhythm, the classic alpha rhythm, is associated with visual cortex, one (the mu rhythm) with the sensory motor cortex around the central sulcus, and yet another (the kappa rhythm) with the auditory cortex.



(B) An electrode on the scalp measures the activity of a very large number of neurons in the underlying regions of the brain, each of which generates a small electrical field that changes over time. This activity (which is thought to be mostly synaptic) makes the more superficial extracellular space negative with respect to deeper cortical regions. The EEG electrode measures a synchronous signal because many thousands of cells are responding in the same manner at more or less the same time. (Adapted from Bear et al., 2001.)

In the 1940s, Edward W. Dempsey and Robert Morrison showed that these EEG rhythms depend in part on activity in the thalamus, since thalamic lesions can reduce or abolish the oscillatory cortical discharge (although some oscillatory activity remains even after the thalamus has been inactivated). At about the same time, H. W. Magoun and G. Moruzzi showed that the reticular activating system in the brainstem is also important in modulating EEG activity. For example, activation of the reticular formation changes the cortical alpha rhythm to beta activity, in association with greater behavioral alertness. In the 1960s, Per Andersen and his colleagues in Sweden further advanced these studies by showing that virtually all areas of the cortex participate in these oscillatory rhythms, which reflect a feedback loop between neurons in the thalamus and cortex (see text).

The cortical origin of EEG activity has been clarified by animal studies, which have shown that the source of the current that causes the fluctuating scalp potential is primarily the pyramidal neurons and their synaptic connections in the deeper layers of the cortex (Figures B and C). (This conclusion was reached by noting the location of electrical field reversal upon passing an electrode vertically through the cortex from surface to white matter.) In general, oscillations come about either because membrane voltage of thalamocortical cells fluctuates spontaneously, or as a result of the reciprocal interaction of excitatory and inhibitory neurons in circuit loops. The oscillations of the EEG are thought to arise from the latter mechanism.

Despite these intriguing observations, the functional significance of these cortical rhythms is not known. The purpose of the brain's remarkable oscillatory activity is a puzzle that has defied electroencephalographers and neurobiologists for more than 60 years.

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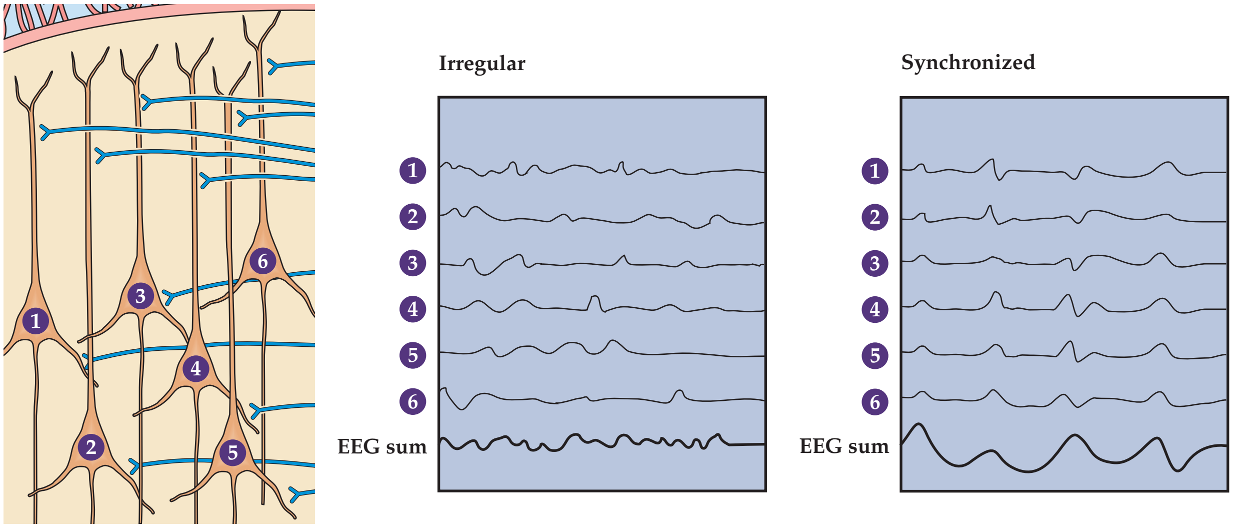
Box C

Electroencephalography *(continued)*



(C) Generation of the synchronous activity that characterizes deep sleep. In the pyramidal cell layer below the EEG electrode, each neuron receives thousands of synaptic inputs. If the inputs are irregular or out of phase, their algebraic sum will have a small amplitude, as occurs in the waking state. If, on the other hand, the neurons at activated at approximately the same time, then the EEG waves will be in phase and the amplitude will be much greater, as occurs in the delta waves that characterize stage IV sleep. (Adapted from Bear et al., 2001.)

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again in the second round of this continuing cycling, but generally not during the rest of the night (see Figure 27.7). On average, four additional periods of REM sleep occur, each having a longer duration.

In summary, the typical 8 hours of sleep experienced each night actually comprise several cycles that alternate between non-REM and REM sleep, and the brain is quite active during much of this supposedly dormant, restful time. The amount of daily REM sleep decreases from about 8 hours at birth to 2 hours at 20 years to only about 45 minutes at 70 years of age (see Figure 27.1B). The reasons for this change over the human lifespan are not known.

Physiological Changes in Sleep States

A variety of additional physiological changes take place during the different stages of sleep (Figure 27.7). Periods of non-REM sleep are characterized by slow, rolling eye movements and by decreases in muscle tone, body movements, heart rate, breathing, blood pressure, metabolic rate and temperature. All these parameters reach their lowest values during stage IV sleep. Periods of REM sleep, in contrast, are accompanied by increases in blood pressure, heart rate, and metabolism to levels almost as high as those found in the awake state. REM sleep, as the name implies, is also characterized by rapid, ballistic eye movements, pupillary constriction, paralysis of many large muscle groups (although obviously not the diaphragm), and the twitching of the smaller muscles in the fingers, toes, and the middle ear. Spontaneous penile erection also occurs during REM sleep, a fact that is clinically important in determining whether a complaint of impotence has a physiological or psychological basis. REM sleep has been observed in all mammals and in at least some birds.

Despite the similarity of EEG recordings obtained in REM sleep and in wakefulness, the two conditions are clearly not equivalent brain states. REM sleep is characterized by dreaming, which entails a sort of visual hallucination, often characterized by increased emotion and a lack of self-reflection and volitional control. Since most muscles are inactive during REM sleep, the motor responses to dreams are relatively minor. (Sleepwalking, which is most common in children from ages 4–12, and sleeptalking actually occur during non-REM sleep and are not usually accompanied or motivated by dreams.) The relative physical paralysis during REM sleep arises from increased activity in GABAergic neurons in the pontine reticular formation that project to inhibitory neurons that synapse in turn with lower motor neurons in the spinal cord (Figure 27.8). Increased activity of descending inhibitory projections from the pons to the dorsal column nuclei also causes a diminished response to somatic sensory stimuli. Taken together, these observations have led to the aphorism that non-REM sleep is characterized by an inactive brain in an active body, whereas REM sleep is characterized by an active brain in an inactive body. Clearly, however, several sensory and motor systems are sequentially activated and inactivated during the different stages of sleep.

The Possible Functions of REM Sleep and Dreaming

Despite this wealth of descriptive information about the stages of sleep and an intense research effort, the functional purposes of the various sleep states remain poorly understood. Whereas most sleep researchers accept the idea that the purpose of non-REM sleep is at least in part restorative, the function of REM sleep remains a matter of considerable controversy.

A possible clue about the purposes of REM sleep is the prevalence of dreams during these epochs of the sleep cycle. The time of occurrence of dreams during sleep was determined by waking volunteers during either non-REM or REM sleep and asking them if they were dreaming. Subjects awakened from REM sleep usually recalled elaborate, vivid and emotional dreams; subjects awakened during non-REM sleep reported fewer dreams, which, when they did occur, were more conceptual, less vivid, and less emo-

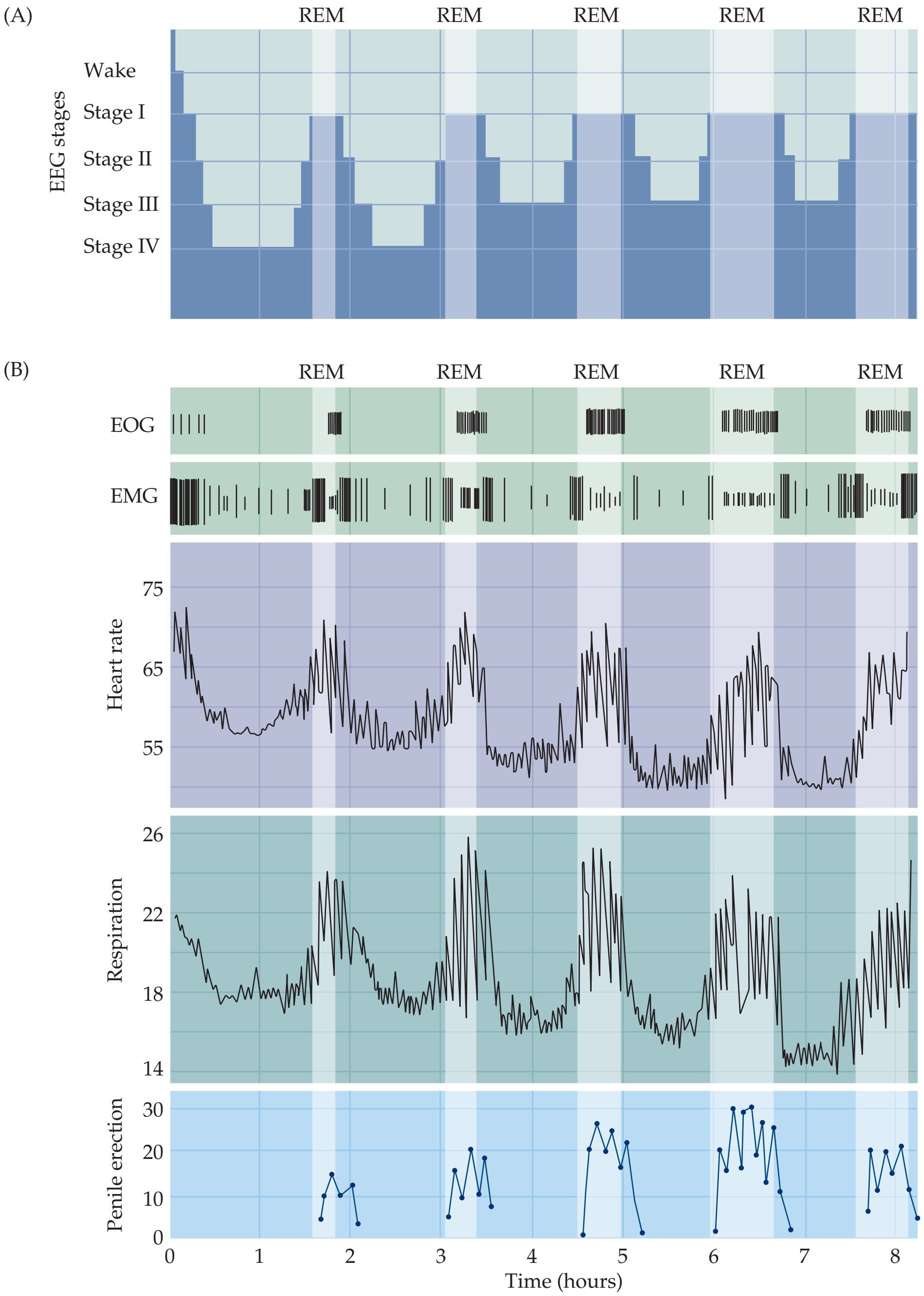
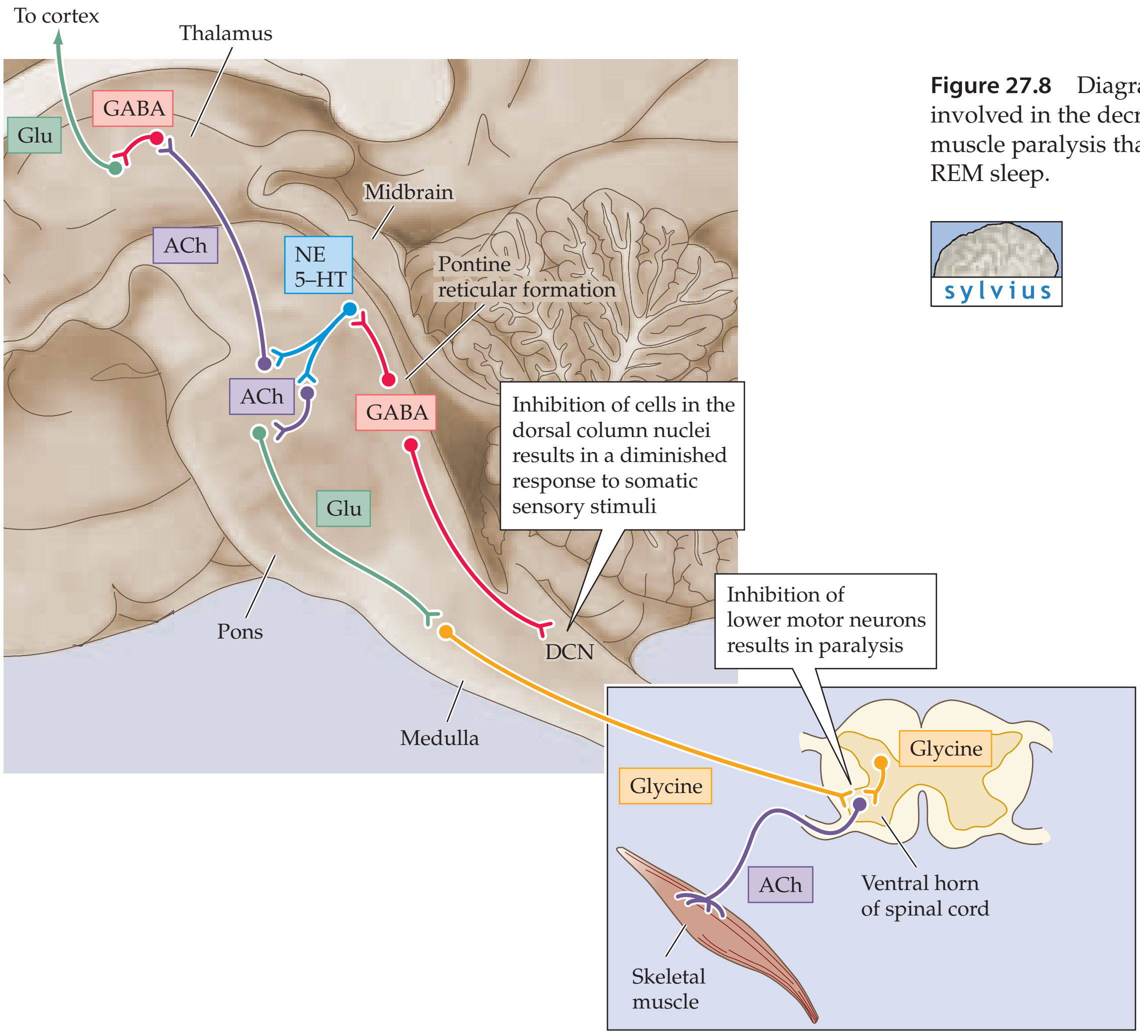


Figure 27.7 Physiological changes in a volunteer during the various sleep states in a typical 8-hour sleep period. (A) The duration of REM sleep increases from 10 minutes in the first cycle to up to 50 minutes in the final cycle; note that slow-wave (stage IV) sleep is attained only in the first two cycles. (B) The upper panels show the electro-oculogram (EOG) and the lower panels show changes in various muscular and autonomic functions. Movement of neck muscles was measured using an electromyogram (EMG). Other than the few slow eye movements approaching stage I sleep, all other eye movements evident in the EOG occur in REM sleep. The greatest EMG activity occurs during the onset of sleep and just prior to awakening. The heart rate (beats per minute) and respiration (breaths per minute) slow in non-REM sleep, but increase almost to the waking levels in REM sleep. Finally, penile erection (strain gauge units) occurs only during REM sleep. (After Foulkes and Schmidt, 1983.)



Inhibition of cells in the dorsal column nuclei results in a diminished response to somatic sensory stimuli

Inhibition of lower motor neurons results in paralysis

Figure 27.8 Diagram of the circuitry involved in the decreased sensation and muscle paralysis that occurs during REM sleep.

tion-laden. Thus dreaming can also occur during light non-REM sleep, near the onset of sleep and before awakening.

Dreams have been studied in a variety of ways, perhaps most notably within the psychoanalytic framework aimed at revealing unconscious thought processes considered to be at the root of neuroses. Sigmund Freud's *The Interpretation of Dreams*, published in 1900, speaks eloquently to the complex relationship between conscious and unconscious mentation. Specifically, Freud thought that during dreaming the "ego" relaxes its hold on the "id," or subconscious. For the most part, these ideas are now out of fashion, but to give Freud his due, at the time he made these speculations little was known about neurobiology of the brain in general and sleep in particular.

Since Freud's time, several other explanations of dreams have been proposed. One idea is that dreaming releases behaviors less commonly entertained in the waking state (e.g., frank aggression). Studies have found that about 60% of dream content is associated with sadness, apprehension, or anger; 20% with happiness or excitement; and (somewhat surprisingly) only 10% with sexual feelings or acts. Another suggestion is that dreaming evolved to dispose of unwanted memories that accumulate during the day. A further plausible idea about the function of dreams is that they help consolidate learned tasks, perhaps by strengthening synaptic activity associated with recent experiences. This hypothesis is supported by studies of remembered spatial location in rodents, and by experiments in humans that show a sleep-dependent improvement in learning. However, some experts, such as Allan Hobson, take the more skeptical view that dream content may be "as much dross as gold, as much cognitive trash as treasure, as much informational noise as a signal of something." Nevertheless, most people, including most sleep researchers, at least privately give some credence to the significance of dream content.

Adding to this uncertainty about the purposes of REM sleep and dreaming is the fact that depriving human subjects of REM sleep for as much as two weeks has little or no obvious effect on their behavior. The apparent innocuousness of REM sleep deprivation contrasts markedly with the devastating effects of total sleep deprivation mentioned earlier. The implication of these findings is that we can get along without REM sleep but need non-REM sleep in order to survive. In summary, the questions of why we have REM sleep and why we dream basically remain unanswered.

Neural Circuits Governing Sleep

From the descriptions of the various physiological states that occur during sleep, it is clear that periodic charges in the balance of excitation and inhibition must occur in many neural circuits. What follows is a brief overview of these incompletely understood circuits and the interactions among them that govern sleeping and wakefulness.

In 1949, Horace Magoun and Giuseppe Moruzzi provided one of the first clues about the circuits involved in the sleep–wake cycle. They found that electrically stimulating a group of cholinergic neurons near the junction of the pons and midbrain causes a state of wakefulness and arousal. This region of the brainstem was given the name **reticular activating system** (Figure 27.9A; see also Box A in Chapter 16). Their work implied that wakefulness requires special activating circuitry—that is, wakefulness is not just the presence of adequate sensory experience. About the same time, the Swiss physiologist Walter Hess found that stimulating the thalamus in an awake cat with low-frequency pulses produced a slow-wave sleep (Figure 27.9B). These seminal experiments showed that sleep entails a patterned interaction between the thalamus and cortex.

The saccade-like eye movements that define REM sleep arise because, in the absence of external visual stimuli, endogenously generated signals from

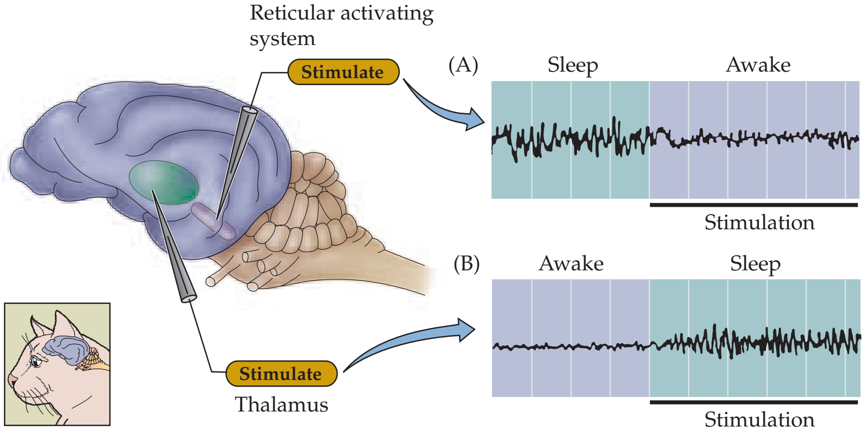


Figure 27.9 Activation of specific neural circuits triggers sleep and wakefulness. (A) Electrical stimulation of the cholinergic neurons near the junction of pons and midbrain (the reticular activating system) causes a sleeping cat to awaken. (B) Slow electrical stimulation of the thalamus causes an awake cat to fall asleep. Graphs show EEG recordings before and during stimulation.

Box D

Consciousness

As the text explains, the mechanisms of sleep and wakefulness determine mental status at any moment on a continuum that normally ranges from stage IV sleep to high alert. There is, however, another way that "wakefulness" has been considered, namely from the perspective of *consciousness* as such. Although the brainstem circuits and projections supporting consciousness are beginning to be understood, these neurological aspects of consciousness are—not surprisingly—insufficient to satisfy philosophers, theologians, and neuroscientists interested in the broader issues that the phenomenon of consciousness raises.

The common concern of these diverse groups is the more general basis of self-awareness, in particular whether other animals have this mental property and whether machines could ever be self-aware in the way humans are. With respect to the first of these issues, despite a longstanding debate about consciousness in other animals, it would be foolish to assert that humans are alone in possessing this obviously useful biological attribute. However, from a purely logical vantage it is impossible, strictly speaking, to know whether any being other than ourselves is conscious; as philosophers have long pointed out, we must inevitably take the consciousness of others on faith (or on the basis of common sense).

Nonetheless, it is reasonable to assume that animals with brains structured much like ours (other primates and, to a considerable degree, mammals generally) have in some measure the same ability to be self-aware as we do. The ability to reflect on the past and plan for the future that is made possible by self-awareness is surely an advantage that evolution would have to some degree inculcated in the very similar brains of higher primates. At what phylogenetic level this assumption about self-awareness falls below the definition of consciousness as we know it in ourselves is, of course, unclear. But a reasonable supposition would be that consciousness is present in animals in proportion to the complexity of their brains and behaviors—particularly those behaviors that are sophisticated enough to benefit from reflecting on past outcomes and future eventualities.

The question of whether machines can ever be conscious is a much more contentious issue, but is also subject to common sense informed by some knowledge of how brains work. If one rejects dualism (the Cartesian proposition that consciousness, or "mind," is an entity beyond the ken of physics, chemistry, and biology, and not therefore subject to the rules of these disciplines), it follows that a structure could be built by sufficiently wise agents that either mimicked our own consciousness by being effectively isomorphic with brains, or achieved consciousness using physically different elements (e.g., computer elements) in sufficiently biological ways to allow self-awareness.

There are, of course, some caveats (not to mention the objections of those people who find such thinking unacceptable on "moral" grounds). An interesting argument in this respect was put forward by the philosopher John Searle to rebut those who imagine that present-day computers, because their operations in some ways resemble mental processes, can already be considered to have the rudiments of consciousness. His famous "Chinese Room" analogy describes a cubicle in which workers are handed English letters that they then translate into Chinese characters. The workers themselves have no knowledge of English or Chinese, but simply a set of rules that enables the characters to be efficiently translated. The output of the room is sensible statements in Chinese. Yet the workers have no knowledge of the meaning of the information they are dealing with or of the room's larger purpose. Searle uses this image to emphasize that meaningful output from a computer, however sophisticated, cannot provide evidence for consciousness or self-awareness within it. Despite this clever argument deflating simplistic assertions that extant machines exhibit a rudimentary form of consciousness, Searle does not dispute the notion that nothing in principle stands in the way of constructing conscious entities.

A great deal of literature on the subject notwithstanding, these fascinating questions about consciousness are not readily subject to neurobiological investigation. Although a number of contemporary scientists have advocated the idea that neurobiology will soon reveal the "basis" of consciousness (Nobel Laureates seem especially prone to this sort of pontification; these include such outspoken individuals as John Eccles, Francis Crick, and Gerald Edelman), such revelations are not likely. A more plausible scenario is that as information grows about the nature of other animals, about computers, and indeed about the brain, the question "What is consciousness?" may simply fade from center stage in much the same way that the question "What is life?" (which stirred up a similar debate early in the twentieth century) was asked less and less frequently as biologists and others recognized it as an ill-posed problem that admitted no definite answer.

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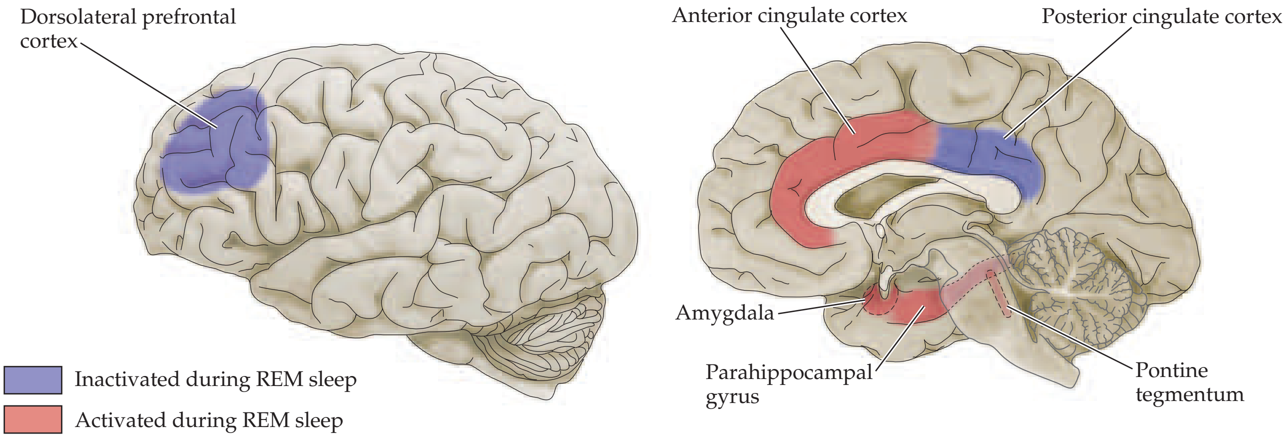

Dorsolateral prefrontal cortex
Anterior cingulate cortex
Posterior cingulate cortex
Amygdala
Parahippocampal gyrus
Pontine tegmentum
🟦 Inactivated during REM sleep
🟥 Activated during REM sleep

Figure 27.10 Diagram showing cortical regions whose activity is increased or decreased during REM sleep. (After Hobson et al., 1989.)

the **pontine reticular formation** are transmitted to the motor region of the superior colliculus. As described in Chapter 19, collicular neurons project to the **paramedialpontine reticular formation (PPRF)** and the **rostral interstitial nucleus**, which coordinates timing and direction of eye movements. REM sleep is also characterized by EEG waves that originate in the pontine reticular formation and propagate through the lateral geniculate nucleus of the thalamus to the occipital cortex. These **pontine-geniculo-occipital (PGO) waves** provide a useful marker for the beginning of REM sleep; they also indicate yet another neural network by which brainstem nuclei can activate the cortex.

Human fMRI and PET (see Box A in Chapter 1) studies have been used to compare brain activity in the awake state and in REM sleep, as well as the phenomenon of consciousness more generally (Box D). Activity in the amygdala, parahippocampus, pontine tegmentum, and anterior cingulate cortex all increase in REM sleep, whereas activity in the dorsolateral prefrontal and posterior cingulate cortices decreases (Figure 27.10). The increase in limbic system activity, coupled with a marked decrease in the influence of the frontal cortex during REM sleep, presumably explains some characteristics of dreams (e.g., their emotionality and their often inappropriate social content; see Chapter 25 for the normal role of the frontal cortex in determining behavior that is appropriate to circumstances in the waking state).

Figure 27.11 Important nuclei in regulation of the sleep–wake cycle. (A) A variety of brainstem nuclei using several different neurotransmitters determines mental status on a continuum that ranges from deep sleep to a high level of alertness. These nuclei include: (left) the cholinergic nuclei of the pons–midbrain junction and the raphe nuclei; and (right) the locus coeruleus and the tuberomammillary nuclues. All have widespread ascending and descending connections to other regions (arrows), which explains their numerous effects. Curved arrows along the perimeter of the cortex indicate the innervation of lateral cortical regions not shown in this plane of section. (B) Location of hypothalamic nuclei involved in sleep. (C) Activation of VLPO induces sleep. Orexin-containing neurons project to different nuclei and produce arousal.

It is generally agreed that a key component of the reticular activating system is a group of **cholinergic nuclei** near the **pons–midbrain junction** that project to thalamocortical neurons (Figure 27.11). The relevant neurons in the nuclei are characterized by high discharge rates during waking and in REM sleep, and by quiescence during non-REM sleep. When stimulated, these nuclei cause "desynchronization" of the electroencephalogram (that is, a shift of EEG activity from high-amplitude, synchronized waves to lower-

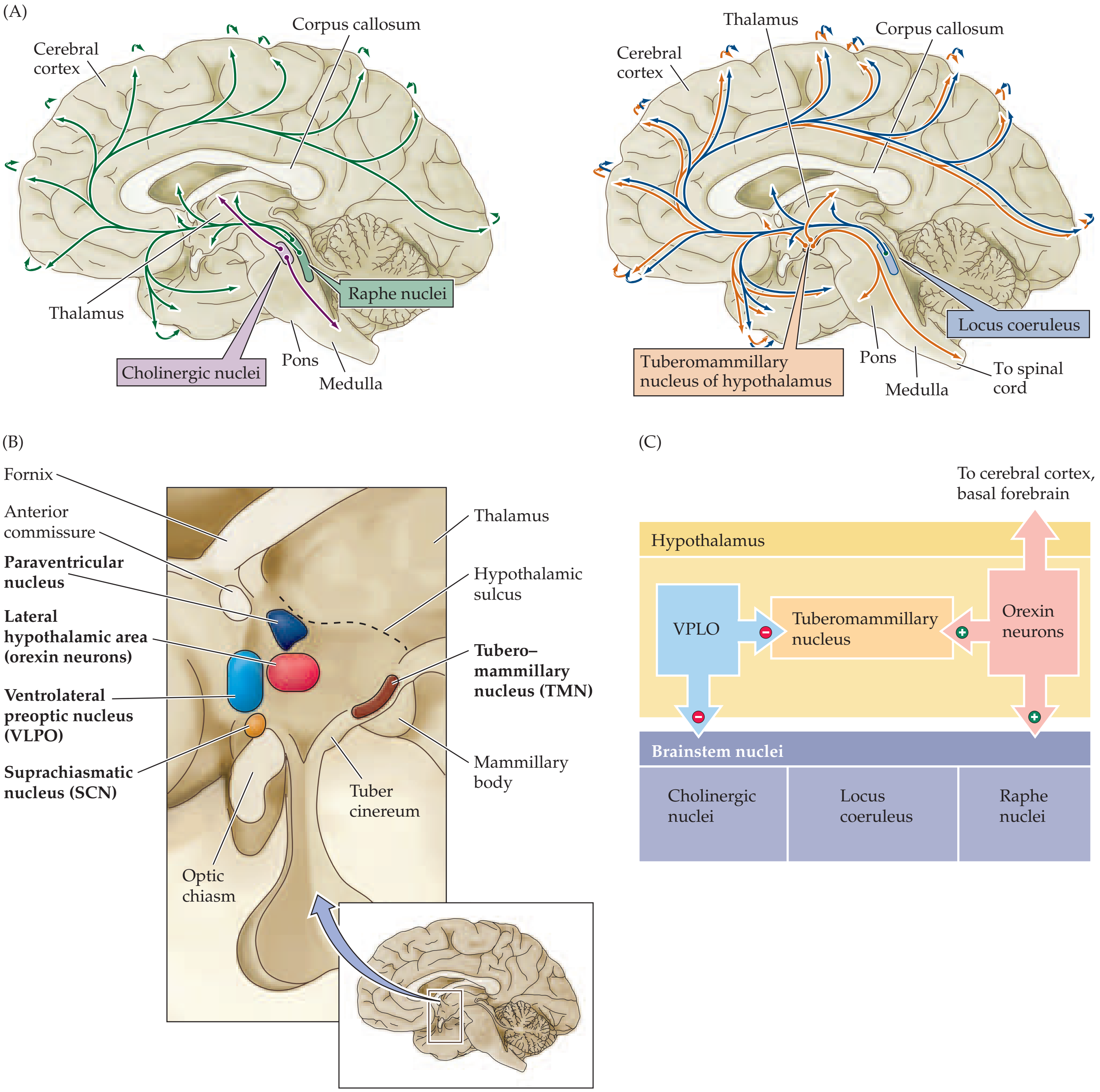

(A)
Cerebral cortex
Corpus callosum
Thalamus
Raphe nuclei
Cholinergic nuclei
Pons
Medulla
Thalamus
Corpus callosum
Cerebral cortex
Locus coeruleus
Tuberomammillary nucleus of hypothalamus
Pons
Medulla
To spinal cord
(B)
Fornix
Anterior commissure
Paraventricular nucleus
Lateral hypothalamic area (orexin neurons)
Ventrolateral preoptic nucleus (VLPO)
Suprachiasmatic nucleus (SCN)
Optic chiasm
Thalamus
Hypothalamic sulcus
Tubero–mammillary nucleus (TMN)
Mammillary body
Tuber cinereum
(C)
To cerebral cortex, basal forebrain
Hypothalamus
VPLO
Tuberomammillary nucleus
Orexin neurons
Brainstem nuclei
Cholinergic nuclei
Locus coeruleus
Raphe nuclei

TABLE 27.1

Summary of the Cellular Mechanisms that Govern Sleep and Wakefulness

Brainstem nuclei responsible	*Neurotransmitter involved*	*Activity state of the relevant brainstem neurons*
WAKEFULNESS		
Cholinergic nuclei of pons-midbrain junction	Acetylcholine	Active
Locus coeruleus	Norepinephrine	Active
Raphe nuclei	Serotonin	Active
Tuberomammillary nuclei	Orexin	Active
NON-REM SLEEP		
Cholinergic nuclei of pons-midbrain junction	Acetylcholine	Decreased
Locus coeruleus	Norepinephrine	Decreased
Raphe nuclei	Serotonin	Decreased
REM SLEEP ON		
Cholinergic nuclei of pons-midbrain junction	Acetylcholine	Active (PGO waves)
Raphe nuclei	Serotonin	Inactive
REM SLEEP OFF		
Locus coeruleus	Norepinephrine	Active

amplitude, higher-frequency, desynchronized ones; see Box C). These features imply that activity of cholinergic neurons in the reticular activating system is a primary cause of wakefulness and REM sleep, and that their relative inactivity is important for producing non-REM sleep.

Activity of these neurons is not, however, the only neuronal basis of wakefulness; also involved are the **noradrenergic neurons of the locus coeruleus**; the **serotonergic neurons of the raphe nuclei;** and the **histamine-containing neurons in the tuberomammillary nucleus (TMN)** of the hypothalamus (Figure 27.11). The activation of these cholinergic, monoaminergic, and histamine-containing networks together produces the awake state. The locus coeruleus and raphe nuclei are modulated by the TMN neurons located near the tuberal region that synthesize the peptide **orexin** (also called **hypercretin**). Orexin promotes waking, and thus may have useful applications in jobs where operators need to stay alert. On the other hand, antihistamines inhibit the histamine-containing TMN network, and thus tend to make people drowsy.

The three circuits responsible for the awake state are periodically inhibited by neurons in the **ventrolateral preoptic nucleus (VLPO)** of the hypothalamus (see Figure 27.11). Thus, activation of VLPO neurons contributes to the onset of sleep, and lesions of VLPO neurons tend to produce insomnia.

These complex interactions and effects are summarized in Table 27.1. Both monoaminergic and cholinergic systems are active during the waking state and suppressed during REM sleep. Thus, decreased activity of the monoaminergic and cholinergic systems leads to the onset of non-REM sleep. In REM sleep, monoaminergic and serotonin neurotransmitter levels markedly decrease, while cholinergic levels increase to approximately the levels found in the awake state.

With so many systems and transmitters involved in the different phases of sleep, it is not surprising that a wide variety of drugs can influence the sleep cycle (Box E).

Thalamocortical Interactions

The effects of brainstem nuclei on mental status are achieved by modulating the rhythmicity of interactions between the thalamus and the cortex. Thus, the activity of several ascending systems from the brainstem decreases both the rhythmic bursting of the thalamocortical neurons and the related synchronized activity of cortical neurons (hence the diminution and ultimate disappearance of high-voltage, low-frequency slow waves during waking and REM sleep; see Box C).

To appreciate how different sleep states reflect modulation of thalamocortical activity, it is useful to consider the electrophysiological responses of the relevant neurons. Thalamocortical neurons receive ascending projections from the locus coeruleus (noradregeneric), raphe nuclei (serotonin), reticular activating system (acetylcholine), TMN (histamine) and, as their name implies, project to cortical pyramidal cells. The primary characteristic of thalamocortical neurons is that they can be in one of two stable electrophysiological states (Figure 27.12): an intrinsic **oscillatory** or **bursting state**, and a **tonically active** or **firing state** that is generated when the neurons are depolarized as occurs when the reticular activating system generates wakefulness; (see Figure 27.11). In the tonic firing state, thalamocortical neurons transmit information to the cortex that is correlated with the spike trains encoding peripheral stimuli. In contrast, when thalamocortical neurons are in the oscillatory/bursting mode, the neurons in the thalamus become synchro-

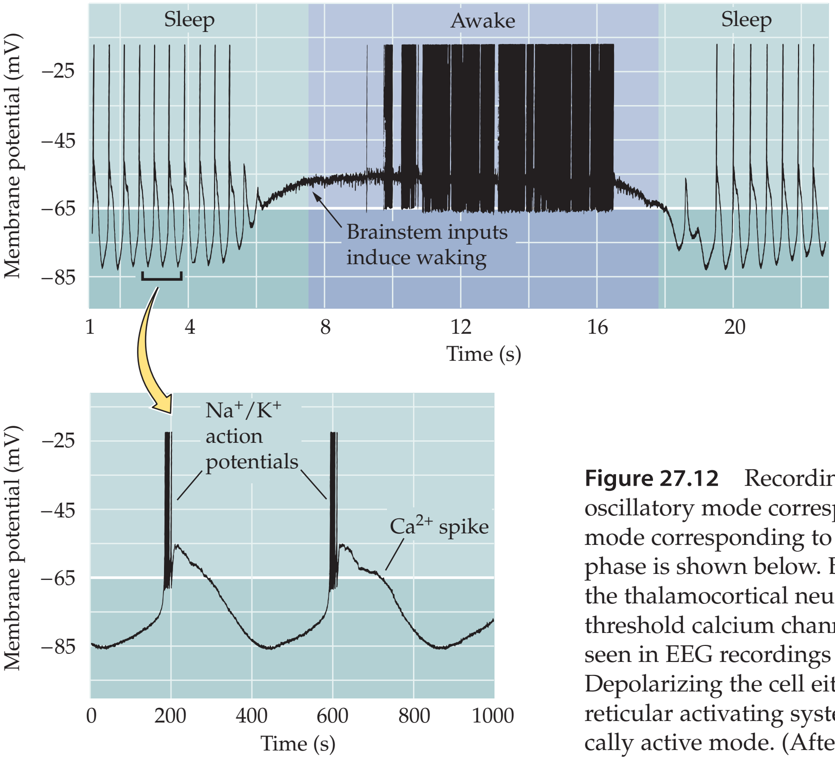


Figure 27.12 Recordings from a thalamocortical neuron, showing the oscillatory mode corresponding to a sleep state, and the tonically active mode corresponding to an awake state. An expanded view of oscillatory phase is shown below. Bursts of action potentials are evoked only when the thalamocortical neuron is hyperpolarized sufficiently to activate low-threshold calcium channels. These bursts account for the spindle activity seen in EEG recordings in stage II sleep (see Figure 27.6 and 27.13). Depolarizing the cell either by injecting current or by stimulating the reticular activating system transforms this oscillatory activity into a tonically active mode. (After McCormick and Pape, 1990.)

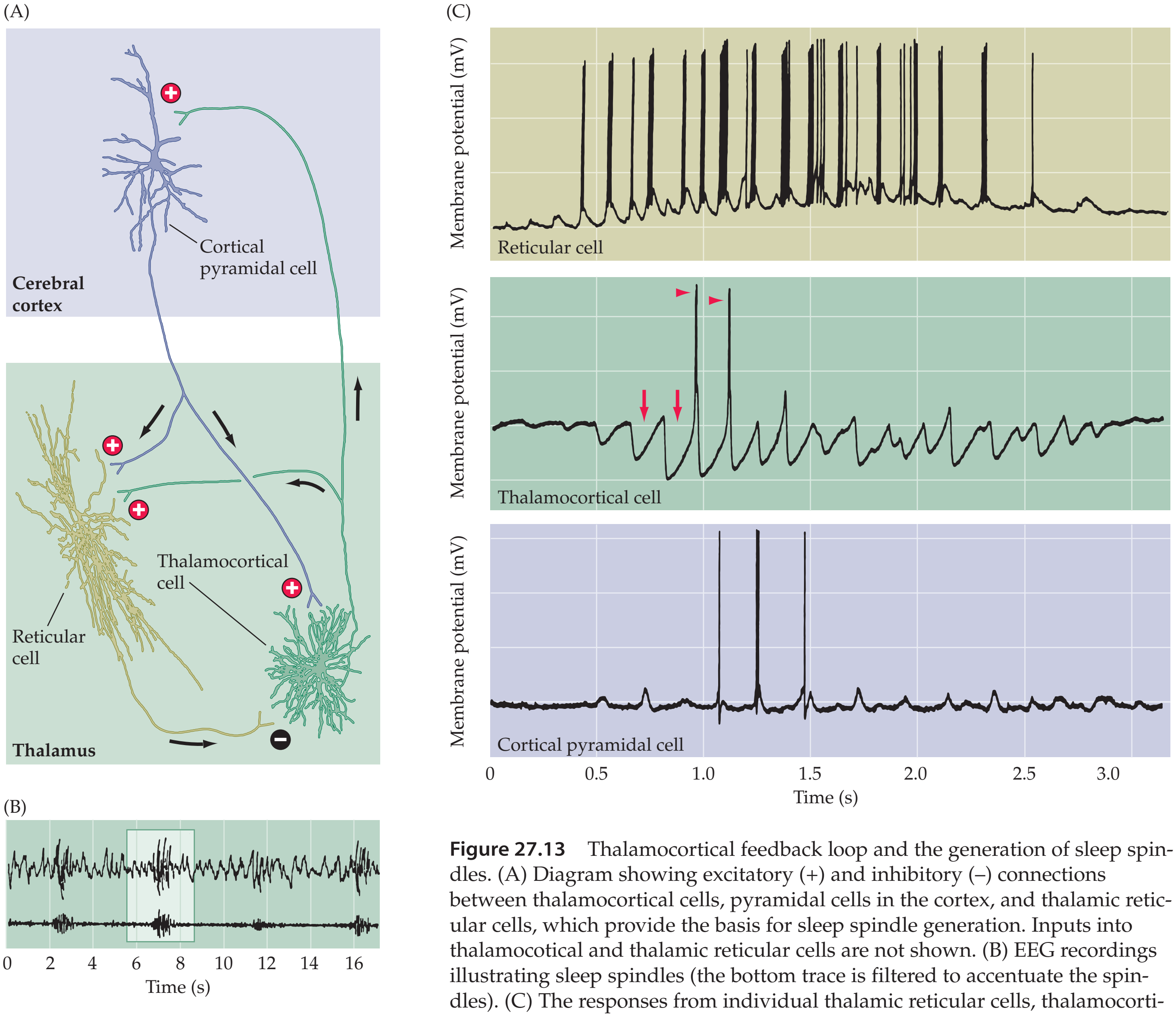


Figure 27.13 Thalamocortical feedback loop and the generation of sleep spindles. (A) Diagram showing excitatory (+) and inhibitory (–) connections between thalamocortical cells, pyramidal cells in the cortex, and thalamic reticular cells, which provide the basis for sleep spindle generation. Inputs into thalamocotical and thalamic reticular cells are not shown. (B) EEG recordings illustrating sleep spindles (the bottom trace is filtered to accentuate the spindles). (C) The responses from individual thalamic reticular cells, thalamocortical cells, and cortical cells during the generation of the middle spindle (boxed in panel B). The bursting behavior of the thalamocortical neurons elicits spikes in cortical cells, which is then evident as spindles in EEG recordings. (After Steriade et al., 1993.)

nized with those in the cortex, essentially "disconnecting" the cortex from the outside world. During slow-wave sleep, when EEG recordings show the lowest frequency and the highest amplitude, this disconnection is maximal.

The oscillatory state of thalamocortical neurons can be transformed into the tonically active state by activity in the cholinergic or monoaminergic projections from the brainstem nuclei (Figure 27.13). Moreover, the oscillatory state is stabilized by hyperpolarizing the relevant thalamic cells. Such hyperpolarization can occur as a consequence of stimulation by GABAergic neurons in the thalamic reticular nucleus. These neurons receive ascending

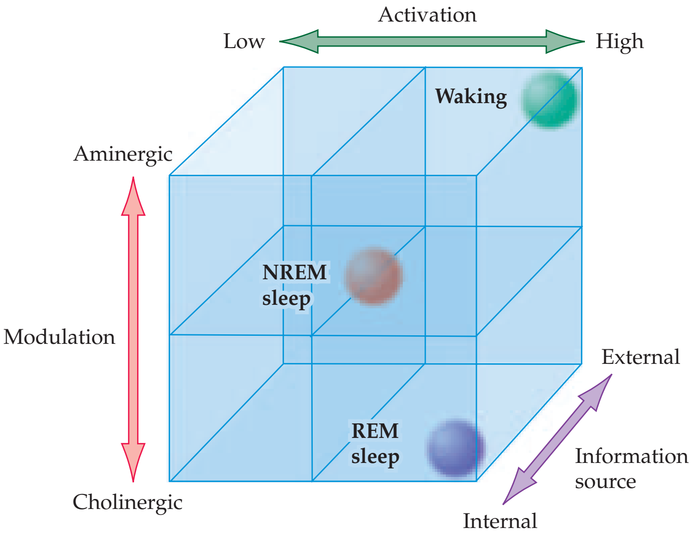


Figure 27.14 Summary scheme of sleep–wake states. In the waking state, activation is high, modulation is aminergic, and the information source is external. In REM sleep, activation is also high, the modulation is cholinergic, and the information source is internal. The other states can likewise be remembered in terms of this general diagram. (After Hobson, 1989.)

information from the brainstem and descending projections from cortical neurons, and they contact the thalamocortical neurons. When neurons in the reticular nucleus undergo a burst of activity, they cause thalamocortical neurons to generate short bursts of action potentials, which in turn generate spindle activity in cortical EEG recordings (indicating a lighter sleep state; see Figures 27.5 and 27.13).

In brief, the control of sleep and wakefulness depends on brainstem and hypothalamic modulation of the thalamus and cortex. It is this thalamocortical loop that generates the EEG signature of mental function along the continuum of deep sleep to high alert. The major components of the brainstem modulatory system are the cholinergic nuclei of the pons–midbrain junction; the noradrenergic cells of the locus coeruleus in the pons; the serotonergic raphe nuclei; and GABAergic neurons in the VLPO. All of these nuclei can exert both direct and indirect effects on the overall cortical activity that determines sleep and wakefulness. The relationship among the various sleep–wake states is summarized in the scheme shown in Figure 27.14.

Sleep Disorders

As noted earlier, an estimated 40% of the U.S. population experiences some kind of sleep disorder during their lifetime. Sleep problems occur more frequently with advancing age and are more prevalent in women than in men. These problems range from simply annoying to life-threatening. The most prevalent problems are insomnia, sleep apnea, “restless legs” syndrome, and narcolepsy.

Insomnia is the inability to sleep for a sufficient length of time (or deeply enough) to produce refreshment. This all-too-common problem has many

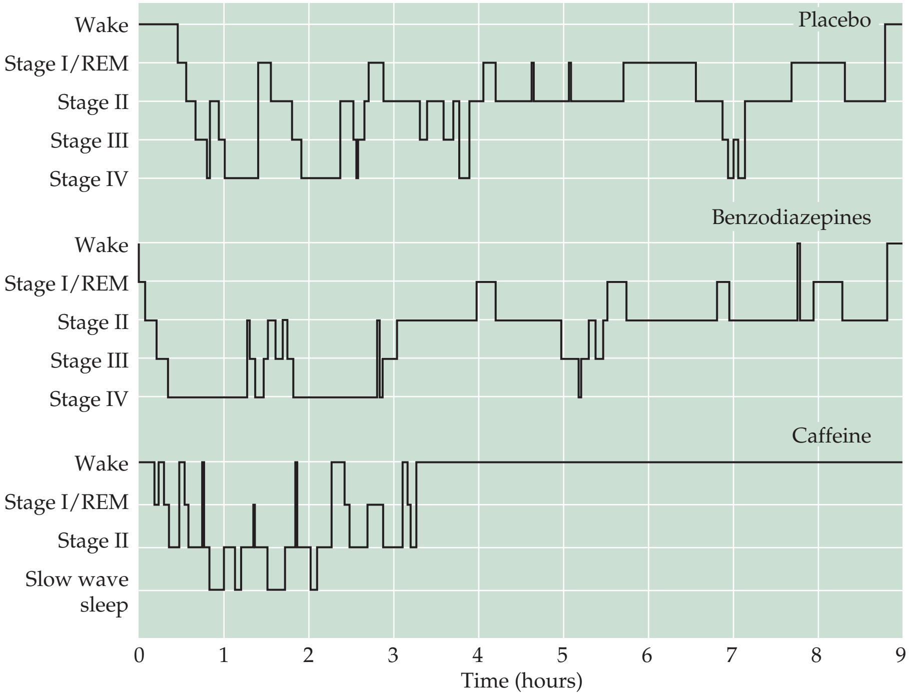
Box E

Drugs and Sleep

It is not surprising that many drugs may affect sleep patterns; the reason is that many neurotransmitters (e.g., acetylcholine, serotonin, norepinepherine, and histamine) are involved in regulating the various states of sleep (see Table 27.1). A simple but useful way of looking at these effects is that in the waking state, the aminergic system is especially active (see Figure 27.14). During non-REM sleep, aminergic and cholinergic input both decrease, but aminergic activity decreases more, such that cholinergic inputs become dominant. Thus there are two major ways drugs alter the sleep pattern: by changing the relative activity of the inputs in any of the three states, or by changing when the different sleep states will commence. For example, insomnia will ensue if, during the waking state, the aminergic input is increased relative to the cholinergic input; in contrast, hypersomnia occurs when there is increased cholinergic activity relative to the aminergic input.

Because of the large number of people who suffer with sleep disorders, numerous drugs are available to treat these problems. One class of commonly used drugs is the benzodiapines. As shown in the figure, these drugs increase the time to onset of the deeper stages of sleep.

Stimulant drugs that prevent sleep are also commonly used, especially caffeine, which is an adenosine receptor antagonist (adenosine induces sleep).



Compared to a placebo, benzodiazepines hasten the onset and depth of sleep, whereas caffeine has the opposite effect.

causes. Short-term insomnia can arise from stress, jet lag, or simply drinking too much coffee. A frequent cause is altered circadian rhythms associated with working night shifts. These problems can usually be prevented by improving sleep habits, avoiding stimulants like caffeine at night, and in some cases taking sleep-promoting medications. More serious insomnia is associated with psychiatric disorders such as depression (see Chapter 28) that presumably affect the balance between the cholinergic, adrenergic, and serotinergic systems that control the onset and duration of the sleep cycles. Long-term insomnia is a particular problem in the elderly, both because aged individuals are subject to more depression and because they frequently take medications that can affect the relevant neurotransmitter systems.

Sleep apnea refers to a pattern of interrupted breathing during sleep that affects about 18 million Americans, most often obese, middle aged males. A person suffering from sleep apnea may wake up dozens or even hundreds of times during the night, with the result that they experience little or no slow-wave sleep and spend less time in REM sleep (Figure 27.15). These individuals are continually tired and often suffer from depression that exacerbates the problem. In some high-risk individuals, sleep apnea may even lead to death from respiratory arrest. The underlying problem is that the airway in susceptible individuals collapses during breathing, thus blocking airflow. In normal sleep, breathing slows and muscle tone decreases throughout the body, including the tone of the pharynx. If the output of the brainstem circuitry regulating commands to the chest wall or to pharyngeal muscles is decreased sufficiently, or if the airway is compressed because of obesity, the pharynx tends to collapse as the muscles relax during the normal cycle of breathing. As a result, oxygen levels decrease and CO_2 levels rise. The rise in CO_2 reflexively causes inspiration, which tends to shift the individual from Stage I sleep to the waking state.

A third sleep disorder is **restless legs syndrome**, a problem that affects about 12 million (mostly elderly) Americans. The characteristic of this syndrome is unpleasant crawling, prickling, or tingling sensations in one or both legs and feet, and an urge to move them about to obtain relief. These sensations occur when the person lies down or sits for prolonged periods of time. The result is constant leg movement during the day and fragmented sleep at night. The neurobiology of this problem is not understood. In mild cases, a hot bath, massaging the legs, or eliminating caffeine may alleviate the problem. In more severe cases, medications such as benzodiazepines may help.

The best-understood sleep disorder is **narcolepsy**, a chronic disorder that affects about 250,000 people (mostly men) in the United States. It is the second leading cause of daytime drowsiness, ranking just behind sleep apnea. Individuals with narcolepsy have frequent "REM sleep attacks" during the day, in which they enter REM sleep from wakefulness without going through non-REM sleep. These "sleep attacks" can last from 30 seconds to 30 minutes or more. The onset of sleep in such individuals can be so abrupt that they fall down, with potentially disastrous consequences; this phenomenon is called *cataplexy*, referring to a temporary loss of muscle control. Insights into the causes of narcolepsy have come from studies of dogs suffer-

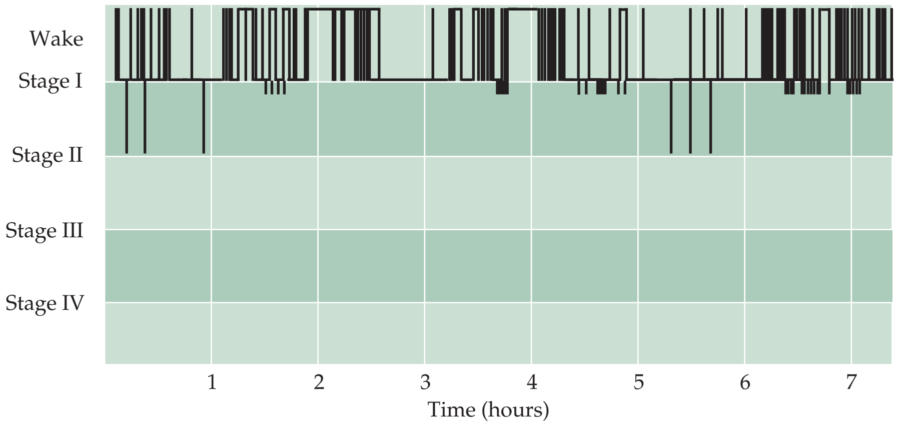


Figure 27.15 Sleep apnea. The sleep pattern of a patient with obstructive sleep apnea. In this condition, patients awake frequently and never descend into stages III or IV sleep. The brief descents below stage I in the record represent short periods of REM sleep. (After Carskadon and Dement, 1989, based on data from G. Nino-Murcia.)

ing from a genetic disorder similar to the human disease. In these animals, narcolepsy is caused by a mutation of the orexin-2 receptor gene (*Orx2*). As already described, orexins are neuropeptides homologous to secretin and are found exclusively in cells in the tuberal region of the hypothalamus, where they project to target nuclei responsible for wakefulness (see Figure 27.11). Evidence from both dogs and mice suggests that the *Orx2* mutation causes hyperexcitability of the neurons that generate REM sleep, and/or impairment of the circuits that inhibit REM sleep. Clinically, narcoleptics are treated using stimulants such as methylphenidate (Ritalin™), amphetamines, or modafanil (Provigil™) to increase their overall level of arousal.

Summary

All animals exhibit a restorative cycle of rest following activity, but only mammals divide the period of rest into distinct phases of non-REM and REM sleep. Why humans (and many other animals) need a restorative phase of suspended consciousness accompanied by decreased metabolism and lowered body temperature is not known. Even more mysterious is why the human brain is periodically active during sleep at levels not appreciably different from the waking state (that is, the neural activity during REM sleep). Despite the electroencephalographic similarities, the psychological states of wakefulness and REM sleep are obviously different. The highly organized sequence of human sleep states is actively generated by nuclei in the brainstem, most importantly the cholinergic nuclei of the pons–midbrain junction, the noradrenergic cells of the locus coeruleus, and the serotonergic neurons of the raphe nuclei. The activity of the relevant cell groups controls the degree of mental alertness on a continuum from deep sleep to waking attentiveness. These brainstem systems are in turn influenced by a circadian clocks located in the suprachiasmatic nucleus and VLPO of the hypothalamus. The clock adjusts periods of sleep and wakefulness to appropriate durations during the 24-hour cycle of light and darkness that is fundamental to life on Earth.

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Chapter 28

Emotions

Overview

The subjective feelings and associated physiological states known as emotions are essential features of normal human experience. Moreover, some of the most devastating psychiatric problems involve emotional (affective) disorders. Although everyday emotions are as varied as happiness, surprise, anger, fear, and sadness, they share some common characteristics. All emotions are expressed through both visceral motor changes and stereotyped somatic motor responses, especially movements of the facial muscles. These responses accompany subjective experiences that are not easily described, but which are much the same in all human cultures. Because emotional expression is closely tied to the visceral motor system, it entails the activity of the central brain structures that govern preganglionic autonomic neurons in the brainstem and spinal cord. Historically, the higher order neural centers that coordinate emotional responses have been grouped under the rubric of the limbic system. More recently, however, several brain regions in addition to the classical limbic system have been shown to play a pivotal role in emotional processing, including the amygdala and several cortical areas in the orbital and medial aspects of the frontal lobe. This broader constellation of cortical and subcortical regions encompasses not only the central components of the visceral motor system but also regions in the forebrain and diencephalon that motivate lower motor neuronal pools concerned with the somatic expression of emotional behavior. Effectively, the concerted action of these diverse brain regions constitutes an emotional motor system. The same forebrain structures that process emotional signals participate in a variety of complex brain functions, including rational decision making, the interpretation and expression of social behavior, and even moral judgments.

Physiological Changes Associated with Emotion

The most obvious signs of emotional arousal involve changes in the activity of the visceral motor (autonomic) system (Chapter 20). Thus, increases or decreases in heart rate, cutaneous blood flow (blushing or turning pale), piloerection, sweating, and gastrointestinal motility can all accompany various emotions. These responses are brought about by changes in activity in the sympathetic, parasympathetic, and enteric components of the visceral motor system, which govern smooth muscle, cardiac muscle, and glands throughout the body. As discussed in Chapter 20, Walter Cannon argued that intense activity of the sympathetic division of the visceral motor system prepares the animal to fully utilize metabolic and other resources in challenging or threatening situations. Conversely, activity of the parasympathetic division (and the enteric division) promotes a building up of metabolic reserves. Cannon further suggested that the natural opposition of the expenditure and storage of resources is reflected in a parallel opposition of the emotions associated with these different physiological states. As Cannon pointed out, "The desire for food and drink, the relish of taking them, all the pleasures of the table are naught in the presence of anger or great anxiety."

Activation of the visceral motor system, particularly the sympathetic division, was long considered an all-or-nothing process. Once effective stimuli engaged the system, it was argued, a widespread discharge of all of its components ensued. More recent studies have shown that the responses of the autonomic nervous system are actually quite specific, with different patterns of activation characterizing different situations and their associated emotional states. Indeed, emotion-specific expressions produced voluntarily can elicit distinct patterns of autonomic activity. For example, if subjects are given muscle-by-muscle instructions that result in facial expressions recognizable as anger, disgust, fear, happiness, sadness, or surprise without being told which emotion they are simulating, each pattern of facial muscle activity is accompanied by specific and reproducible differences in visceral motor activity (as measured by indices such as heart rate, skin conductance, and skin temperature). Moreover, autonomic responses are strongest when the facial expressions are judged to most closely resemble actual emotional expression and are often accompanied by the subjective experience of that emotion. One interpretation of these findings is that when voluntary facial expressions are produced, signals in the brain engage not only the motor cortex but also some of the circuits that produce emotional states. Perhaps this relationship helps explain how good actors can be so convincing. Nevertheless, we are quite adept at recognizing the difference between a contrived facial expression and the spontaneous smile that accompanies a pleasant emotional state (Box A).

This evidence, along with many other observations, indicates that one source of emotion (but certainly not the only source) is sensory drive from muscles and internal organs. This input forms the sensory limb of reflex circuitry that allows rapid physiological changes in response to altered conditions. However, physiological responses can also be elicited by complex and idiosyncratic stimuli mediated by the forebrain. For example, an anticipated tryst with a lover, a suspenseful episode in a novel or film, stirring patriotic or religious music, or dishonest accusations can all lead to autonomic activation and strongly felt emotions. The neural activity evoked by such complex stimuli is relayed from the forebrain to visceral and somatic motor nuclei via the hypothalamus and brainstem reticular formation, the major structures that coordinate the expression of emotional behavior (see the next section).

In summary, emotion and sensorimotor behavior are inextricably linked. As William James put it more than a century ago:

> What kind of an emotion of fear would be left if the feeling neither of quickened heart-beats nor of shallow breathing, neither of trembling lips nor of weakened limbs, neither of goose-flesh nor of visceral stirrings, were present, it is quite impossible for me to think … I say that for us emotion dissociated from all bodily feeling is inconceivable.
>
> William James, 1893 (*Psychology*: p. 379.)

The Integration of Emotional Behavior

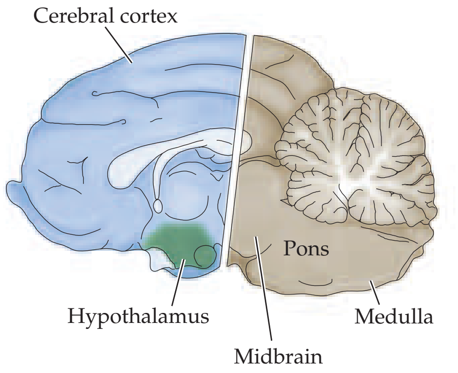
In 1928, Phillip Bard reported the results of a series of experiments that pointed to the hypothalamus as a critical center for coordination of both the visceral and somatic motor components of emotional behavior (see Box A in Chapter 20). Bard removed both cerebral hemispheres (including the cortex, underlying white matter, and basal ganglia) in a series of cats. When the anesthesia had worn off, the animals behaved as if they were enraged. The angry behavior occurred spontaneously and included the usual autonomic correlates of this emotion: increased blood pressure and heart rate, retraction of the nictitating membranes (the thin connective tissue sheets associated with feline eyelids), dilation of the pupils, and erection of the hairs on the back and tail. The cats also exhibited somatic motor components of anger, such as arching the back, extending the claws, lashing the tail, and snarling. This behavior was called **sham rage** because it had no obvious target. Bard showed that a complete response occurred as long as the caudal hypothalamus was intact (Figure 28.1). Sham rage could not be elicited, however, when the brain was transected at the junction of the hypothalamus and midbrain (although some uncoordinated components of the response were still apparent). Bard suggested that whereas the subjective experience of emotion might depend on an intact cerebral cortex, the expression of coordinated emotional behaviors does not necessarily entail cortical processes. He also emphasized that emotional behaviors are often directed toward self-preservation (a point made by Charles Darwin in his classic book on the evolution of emotion), and that the functional importance of emotions in all mammals is consistent with the involvement of phylogenetically older parts of the nervous system.

Complementary results were reported by Walter Hess, who showed that electrical stimulation of discrete sites in the hypothalamus of awake, freely moving cats could also lead to a rage response, and even to subsequent attack behavior. Moreover, stimulation of other sites in the hypothalamus caused a defensive posture that resembled fear. In 1949, a share of the Nobel Prize in Physiology or Medicine was awarded to Hess "for his discovery of the functional organization of the interbrain [hypothalamus] as a coordinator of the activities of the internal organs." Experiments like those of Bard and Hess led to the important conclusion that the basic circuits for organized behaviors accompanied by emotion are in the diencephalon and the brainstem structures connected to it. Furthermore, their work emphasized that the control of the involuntary motor system is not entirely separable from the control of the voluntary pathways, an important consideration in understanding the motor aspects of emotion, as discussed below.

The routes by which the hypothalamus and other forebrain structures influence the visceral and somatic motor systems are complex. The major targets of the hypothalamus lie in the **reticular formation**, the tangled web of nerve cells and fibers in the core of the brainstem (see Box A in Chapter 16). This structure contains over 100 identifiable cell groups, including some of the nuclei that control the brain states associated with sleep and wakefulness described in the previous chapter. Other important circuits in the reticular formation control cardiovascular function, respiration, urination, vomiting, and swallowing. The reticular neurons receive hypothalamic input from and feed into both somatic and autonomic effector systems in the brainstem and spinal cord. Their activity can therefore produce widespread visceral motor and somatic motor responses, often overriding reflex function and sometimes involving almost every organ in the body (as implied by Cannon's dictum about the sympathetic preparation of the animal for fight or flight).

In addition to the hypothalamus, other sources of descending projections from the forebrain to the brainstem reticular formation contribute to the

(A) No "sham rage"



(B) "Sham rage" remains

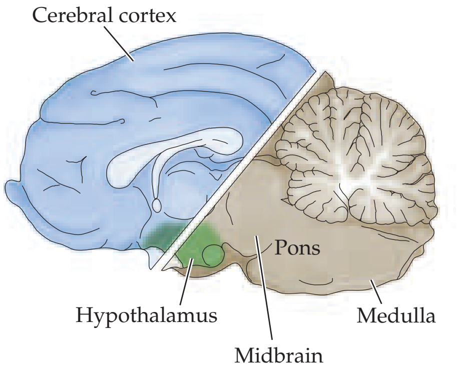


Figure 28.1 Midsagittal view of a cat's brain, illustrating the regions sufficient for the expression of emotional behavior. (A) Transection through the midbrain, disconnecting the hypothalamus and brainstem, abolishes "sham rage." (B) The integrated emotional responses associated with "sham rage" survive removal of the cerebral hemispheres as long as the caudal hypothalamus remains intact. (After LeDoux, 1987.)

Box A

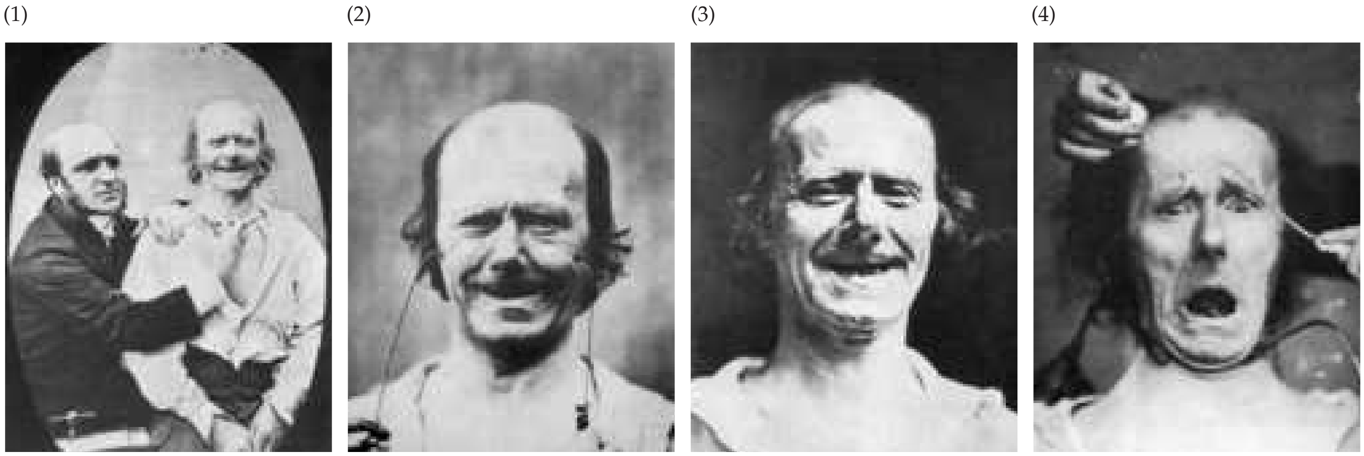
Facial Expressions: Pyramidal and Extrapyramidal Contributions

In 1862, the French neurologist and physiologist G.-B. Duchenne de Boulogne published a remarkable treatise on facial expressions. His work was the first to systematically examine the contributions of small groups of cranial muscles to the expressions that communicate the richness of human emotion. Duchenne reasoned that “one would be able, like nature herself, to paint the expressive lines of the emotions of the soul on the face of man.” In so doing, he sought to understand how the coordinated contractions of groups of muscles express distinct, pan-cultural emotional states. To achieve this goal, he pioneered the use of transcutaneous electrical stimulation (then called “faradization” after the British chemist and physicist Michael Faraday) to activate single muscles and small groups of muscles in the face, dorsal surface of the head, and neck. Duchenne also documented the faces of his subjects with another technological innovation: photography (Figure A). His seminal contribution was the identification of muscles and muscle groups, such as the obicularis oculi, that cannot be activated by force of the will, but are only “put into play by the sweet emotions of the soul.” Duchenne concluded that the emotion-driven contraction of these muscle groups surrounding the eyes, together with the zygomaticus major, convey the genuine experience of happiness, joy and laughter. In recognition of these insights, psychologists sometimes refer to this facial expression as the “Duchenne smile.”

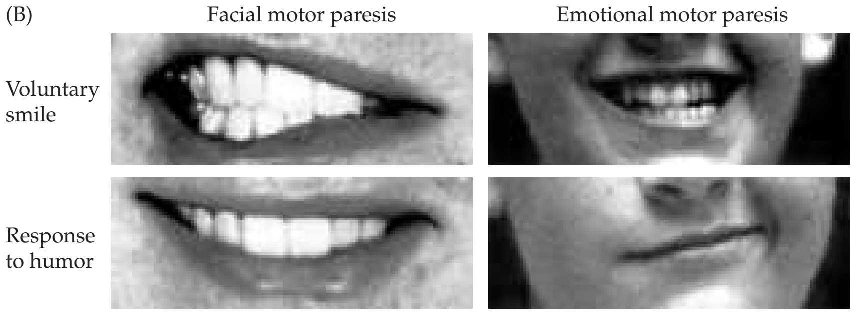
In normal individuals, such as the Parisian shoemaker illustrated in Figure A, the difference between a forced smile (produced by voluntary contraction or electrical stimulation of facial muscles) and a spontaneous (emotional) smile testifies to the convergence of descending motor signals from different forebrain centers onto premotor and motor neurons in the brainstem that control the facial musculature. In contrast to the Duchenne smile, the contrived smile of volition (sometimes called a “pyramidal smile”) is driven by the motor cortex, which communicates with the brainstem and spinal cord via the pyramidal tracts. The Duchenne smile is motivated by accessory motor areas in the prefrontal cortex (see Box B in Chapter 16) and ventral parts of the basal ganglia that access brainstem nuclei via multisynaptic, “extrapyramidal” pathways through the brainstem reticular formation.

Studies of patients with specific neurological injury to these separate descending systems of control have further differentiated the forebrain centers responsible for control of the muscles of facial expression (Figure B). Patients with unilateral facial paralysis due to damage of descending pathways from the motor cortex (upper motor neuron syndrome; see Chapter 16) have considerable difficulty moving their lower facial muscles on one side, either voluntarily or in response to commands, a condition called voluntary facial paresis (Figure B, left panels). Nonetheless, many such

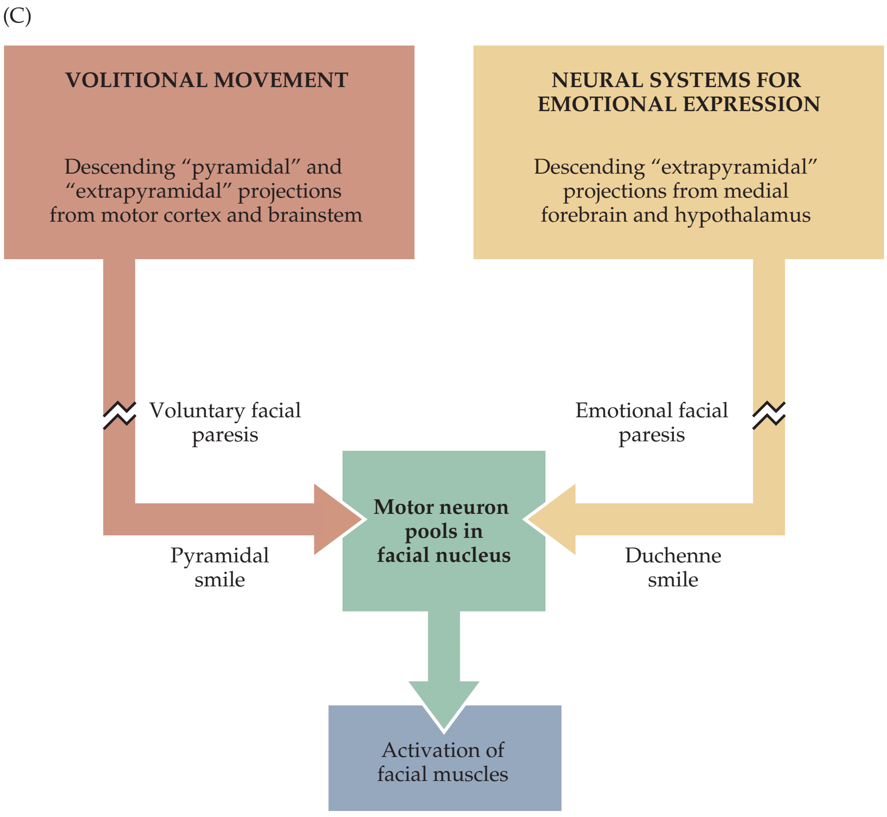
(A)



(A) Duchenne and one of his subjects undergoing “faradization” of the muscles of facial expression (1). Bilateral electrical stimulation of the zygomaticus major mimicked a genuine expression of happiness (2), although closer examination shows insufficient contraction of the obicularis oculi (surrounding the eyes) compared to spontaneous laughter (3). Stimulation of the brow and neck produced an expression of “terror mixed with pain, torture … that of the damned” (4); however, the subject reported no discomfort or emotional experience consistent with the evoked contractions.


(B)
Facial motor paresis
Emotional motor paresis
Voluntary smile
Response to humor

(B) Left panels: Mouth of a patient with a lesion that destroyed descending fibers from the right motor cortex displaying voluntary facial paresis. When asked to show her teeth, the patient was unable to contract the muscles on the left side of her mouth (upper left), yet her spontaneous smile in response to a humorous remark is nearly symmetrical (lower left). Right panels: Face of a child with a lesion of the left forebrain that interrupted descending pathways from nonclassical motor cortical areas, producing emotional facial paresis. When asked to smile volitionally, the contractions of the facial muscles are nearly symmetrical (upper right). In spontaneous response to a humorous comment, however, the right side of the patient's face fails to express emotion (lower right).


(C)
VOLITIONAL MOVEMENT
Descending "pyramidal" and "extrapyramidal" projections from motor cortex and brainstem
NEURAL SYSTEMS FOR EMOTIONAL EXPRESSION
Descending "extrapyramidal" projections from medial forebrain and hypothalamus
Voluntary facial paresis
Emotional facial paresis
Motor neuron pools in facial nucleus
Pyramidal smile
Duchenne smile
Activation of facial muscles

(C) The complementary deficits demonstrated in Figure B are explained by selective lesions of one of two anatomically and functionally distinct sets of descending projections that motivate the muscles of facial expression.

individuals produce symmetrical *involuntary* facial movements when they laugh, frown, or cry in response to amusing or distressing stimuli. In such patients, pathways from regions of the forebrain other than the classical motor cortex in the posterior frontal lobe remain available to activate facial movements in response to stimuli with emotional significance.

A much less common form of neurological injury, called emotional facial paresis, demonstrates the opposite set of impairments, i.e., loss of the ability to express emotions by using the muscles of the face without loss of volitional control (Figure B, right panels). Such individuals are able to produce symmetrical pyramidal smiles, but fail to display spontaneous emotional expressions involving the facial musculature contralateral to the lesion. These two systems are diagrammed in Figure C.

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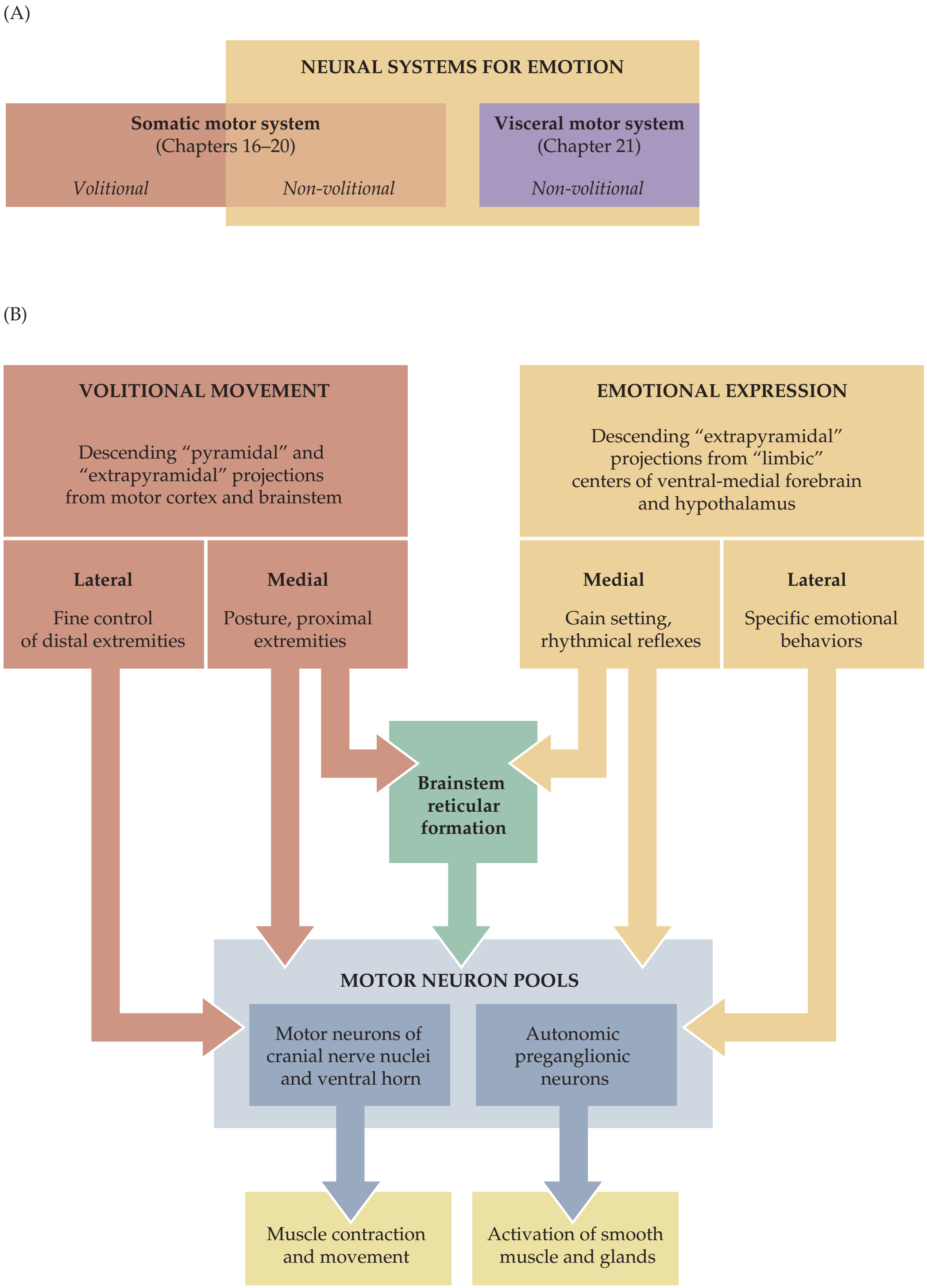
(A)
NEURAL SYSTEMS FOR EMOTION
Somatic motor system
(Chapters 16–20)
Volitional
Non-volitional
Visceral motor system
(Chapter 21)
Non-volitional
(B)
VOLITIONAL MOVEMENT
Descending "pyramidal" and "extrapyramidal" projections from motor cortex and brainstem
Lateral
Fine control of distal extremities
Medial
Posture, proximal extremities
EMOTIONAL EXPRESSION
Descending "extrapyramidal" projections from "limbic" centers of ventral-medial forebrain and hypothalamus
Medial
Gain setting, rhythmical reflexes
Lateral
Specific emotional behaviors
Brainstem reticular formation
MOTOR NEURON POOLS
Motor neurons of cranial nerve nuclei and ventral horn
Autonomic preganglionic neurons
Muscle contraction and movement
Activation of smooth muscle and glands

expression of emotional behavior. Collectively, these additional centers in the forebrain are considered part of the **limbic system**, which is described in the following section. These descending influences on the expression of somatic and visceral motor behavior arise outside of the classic motor cortical areas in the posterior frontal lobe.

◀ **Figure 28.2** Components of the nervous system that organize the expression of emotional experience. (A) The neural systems that help convey emotion include forebrain centers that govern the nonvolitional expression of somatic motor behavior and the visceral motor system. (B) Diagram of the descending systems that control somatic and visceral motor effectors. Motor cortical areas in the posterior frontal lobe give rise to descending projections that, together with secondary projections arising in the brainstem, are organized into medial and lateral components. As described in Chapter 16, these descending projections account for volitional somatic movements. Functionally and anatomically distinct centers in the forebrain govern the expression of nonvolitional somatic motor and visceral motor functions, which are coordinated to meditate emotional behavior. "Limbic" centers in the ventral-medial forebrain and hypothalamus also give rise to medial and lateral descending projections. For both systems of descending projections, the lateral components elicit specific behaviors (e.g., volitional digit movements and emotional facial expressions), while the medial components support and modulate the execution of such behaviors. The descending projections of both systems terminate in several integrative centers in the brainstem reticular formation, as well as the motor neuronal pools of the brainstem and spinal cord. In addition, the limbic forebrain centers innervate components of the visceral motor system that govern preganglionic autonomic neurons in the brainstem and spinal cord.

Thus, the descending control of emotional expression entails two parallel systems that are anatomically and functionally distinct (Figure 28.2). The voluntary motor component described in detail in Chapters 15 through 20 comprises the classical motor areas of the posterior frontal lobe and related circuitry in the basal ganglia and cerebellum. The descending pyramidal and extrapyramidal projections from the motor cortex and brainstem ultimately convey the impulses responsible for voluntary somatic movements. In addition to the descending systems that govern volitional movements, several cortical and subcortical structures in the medial frontal lobe and ventral parts of the forebrain, including related circuitry in the ventral part of the basal ganglia and hypothalamus, give rise to separate descending projections that run parallel to the pathways of the volitional motor system. These descending projections of the medial and ventral forebrain terminate on visceral motor centers in the brainstem reticular formation, preganglionic autonomic neurons, and certain somatic premotor and motor neuron pools that also receive projections from volitional motor centers. The two types of facial paresis illustrated in Box A underscore this dual nature of descending motor control.

In short, the somatic and visceral activities associated with unified emotional behavior are mediated by the activity of both the somatic and visceral motor neurons, which integrate parallel, descending inputs from a constellation of forebrain sources. The remaining sections of the chapter are devoted to the organization and function of the forebrain centers that specifically govern the experience and expression of emotional behavior.

The Limbic System

Attempts to understand the effector systems that control emotional behavior have a long history. In 1937, James Papez (pronouced "Papes") first proposed that specific brain circuits are devoted to emotional experience and expression (much as the occipital cortex is devoted to vision, for instance). In seeking to understand what parts of the brain serve this function, he began to explore

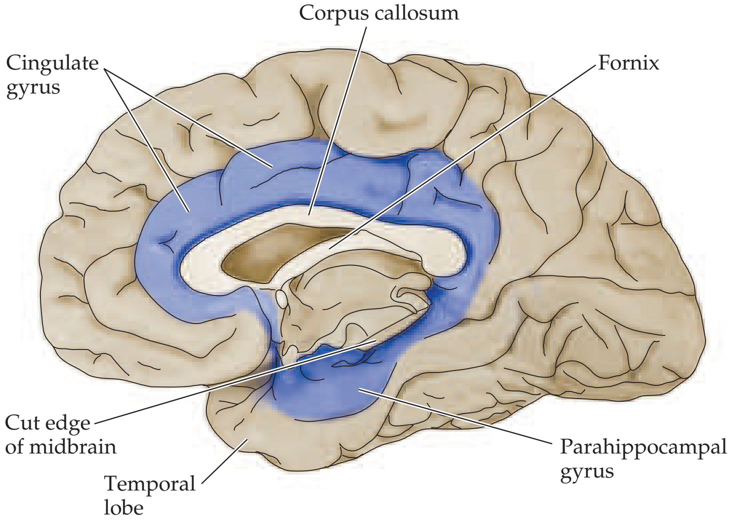

Figure 28.3 The so-called limbic lobe includes the cortex on the medial aspect of the cerebral hemisphere that forms a rim around the corpus callosum and diencephalon, including the cingulate gyrus (lying above the corpus callosum) and the parahippocampal gyrus. Historically, the olfactory bulb and olfactory cortex (not illustrated here) have also been considered to be important elements of the limbic lobe.

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the medial aspects of the cerebral hemisphere. In the 1850s, Paul Broca used the term "limbic lobe" to refer to the part of the cerebral cortex that forms a rim (*limbus* is Latin for rim) around the corpus callosum and diencephalon on the medial face of the hemispheres (Figure 28.3). Two prominent components of this region are the **cingulate gyrus**, which lies above the corpus callosum, and the **parahippocampal gyrus**, which lies in the medial temporal lobe.

For many years, these structures, along with the olfactory bulbs, were thought to be concerned primarily with the sense of smell. Indeed, Broca considered the olfactory bulbs to be the principal source of input to the limbic lobe. Papez, however, speculated that the function of the limbic lobe might be more related to emotions. He knew from the work of Bard and Hess that the hypothalamus influences the expression of emotion; he also knew, as everyone does, that emotions reach consciousness, and that higher cognitive functions affect emotional behavior. Ultimately, Papez showed that the cingulate cortex and hypothalamus are interconnected via projections from the **mammillary bodies** (part of the posterior hypothalamus) to the **anterior nucleus of the dorsal thalamus**, which projects in turn to the **cingulate gyrus.** The cingulate gyrus (and many other cortical regions as well) projects to the **hippocampus**. Finally, he showed that the hippocampus projects via the **fornix** (a large fiber bundle) back to the hypothalamus. Papez suggested that these pathways provided the connections necessary for cortical control of emotional expression, and they became known as the "Papez circuit."

Over time, the concept of a forebrain circuit for the control of emotional expression, first elaborated by Papez, has been revised to include parts of the **orbital and medial prefrontal cortex**, **ventral parts of the basal ganglia**, **the mediodorsal nucleus of the thalamus** (a different thalamic nucleus than the one emphasized by Papez), and a large nuclear mass in the temporal lobe anterior to the hippocampus, called the **amygdala**. This set of structures, together with the parahippocampal gyrus and cingulate cortex, is generally referred to as the **limbic system** (Figure 28.4). Thus, some of the structures that Papez originally described (the hippocampus, for example) now appear to have little to do with emotional behavior, whereas the amygdala, which was hardly mentioned by Papez, clearly plays a major role in the experience and expression of emotion (Box B).

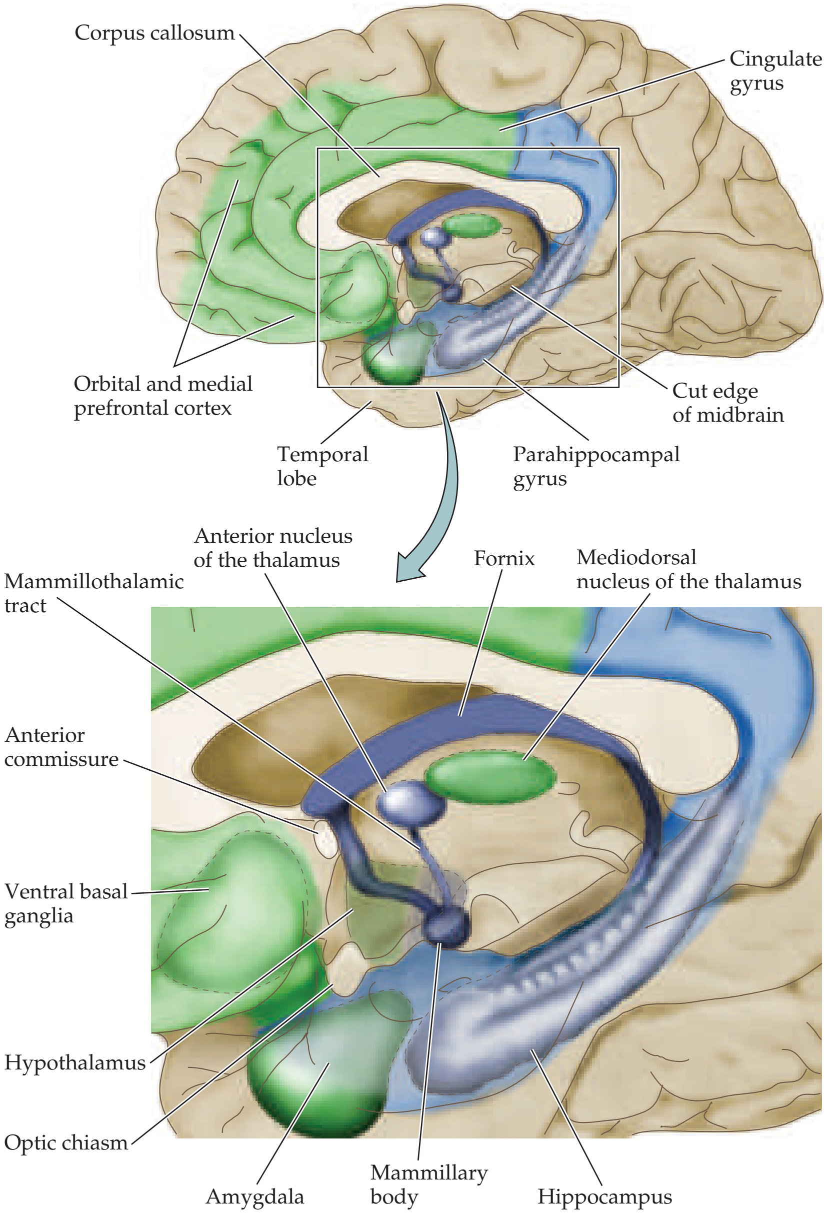
Corpus callosum
Cingulate gyrus
Orbital and medial prefrontal cortex
Temporal lobe
Parahippocampal gyrus
Cut edge of midbrain
Anterior nucleus of the thalamus
Fornix
Mediodorsal nucleus of the thalamus
Mammillothalamic tract
Anterior commissure
Ventral basal ganglia
Hypothalamus
Optic chiasm
Amygdala
Mammillary body
Hippocampus

Figure 28.4 Modern conception of the limbic system. Two especially important components of the limbic system not emphasized in early anatomical accounts are the orbital and medial prefrontal cortex and the amygdala. These two telencephalic regions, together with related structures in the thalamus, hypothalamus and ventral striatum, are especially important in the experience and expression of emotion (colored green). Other parts of the limbic system, including the hippocampus and the mammillary bodies of the hypothalamus, are no longer considered important neural centers for processing emotion (colored blue).

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About the same time that Papez proposed that these structures were important for the integration of emotional behavior, Heinrich Klüver and Paul Bucy were carrying out a series of experiments on rhesus monkeys in which they removed a large part of both medial temporal lobes, thus destroying much of the limbic system. They reported a set of abnormal behaviors in these animals that is now known as the Klüver-Bucy syndrome (Box C). Among the most prominent changes was visual agnosia: the animals appeared to be unable to recognize objects, although they were not blind, a deficit similar to that sometimes seen in human patients following lesions of the temporal cortex (see Chapter 25). In addition, the monkeys displayed bizarre oral behaviors. For instance, these animals would put objects into their mouths that normal monkeys would not. They exhibited hyperactivity and hypersexuality, approaching and making physical contact with

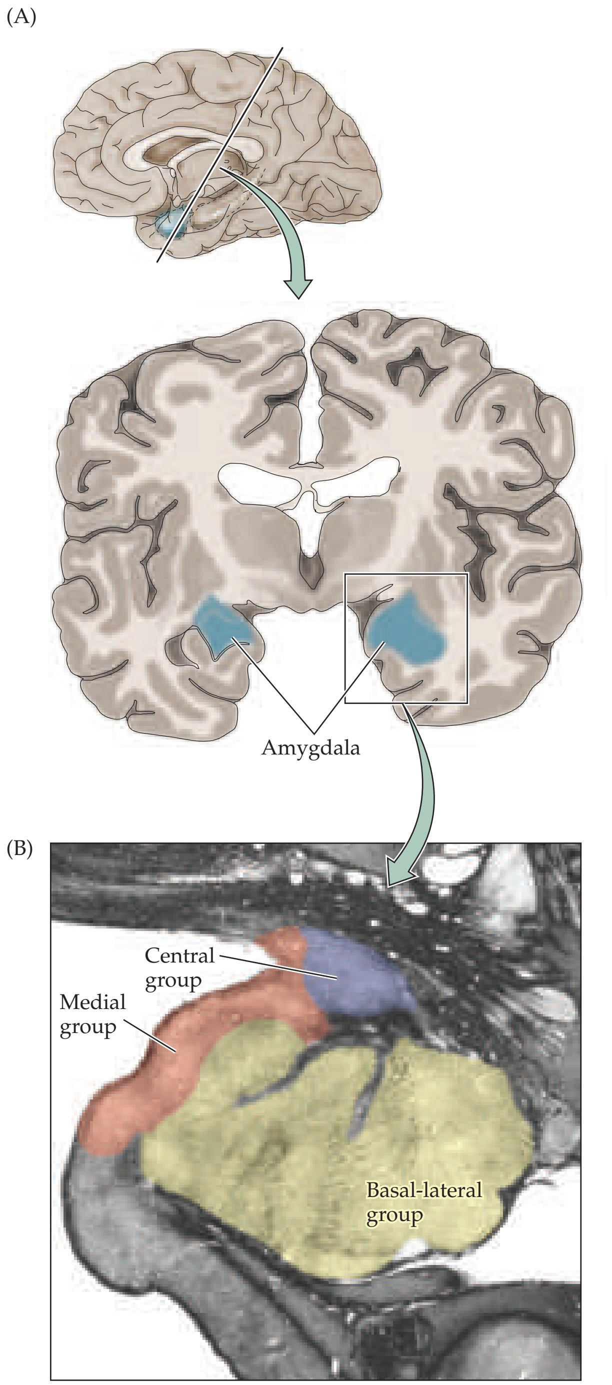
Box B

The Anatomy of the Amygdala

The amygdala is a complex mass of gray matter buried in the anterior-medial portion of the temporal lobe, just rostral to the hippocampus (Figure A). It comprises multiple, distinct subnuclei and cortical regions that are richly connected to other nearby cortical areas on the ventral and medial aspect of the hemispheric surface. The amygdala (or amygdaloid complex, as it is often called) can best be thought of in terms of three major functional and anatomical subdivisions, each of which has a unique set of connections with other parts of the brain (Figures B and C). The medial group of subnuclei has extensive connections with the olfactory bulb and the olfactory cortex. The basal-lateral group, which is especially large in humans, has major connections with the cerebral cortex, especially the orbital and medial prefrontal cortex of the frontal lobe and the associational cortex of the anterior temporal lobe. The central and anterior group of nuclei is characterized by connections with the hypothalamus and brainstem, including such visceral sensory structures as the nucleus of the solitary tract and the parabrachial nucleus.

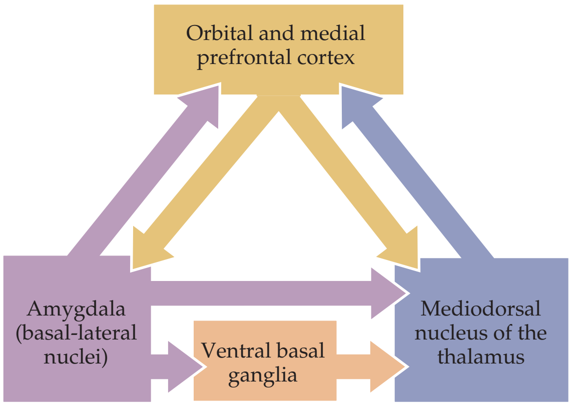
The amygdala thus links cortical regions that process sensory information with hypothalamic and brainstem effector systems. Cortical inputs provide information about highly processed visual, somatic sensory, visceral sensory, and auditory stimuli. These pathways from sensory cortical areas distinguish the amygdala from the hypothalamus, which receives relatively unprocessed visceral sensory inputs. The amygdala also receives sensory input directly from some thalamic nuclei, the olfactory bulb, and visceral sensory relays in the brainstem.

Physiological studies have confirmed this convergence of sensory information. Thus, many neurons in the amygdala respond to visual, auditory, somatic



(A) Coronal section through the forebrain at the level of the amygdala; box indicates the region illustrated in panel (B). (B) Histological section through the human amygdala, stained with silver salts to reveal the presence of myelinated fiber bundles. These bundles subdivide major nuclei and cortical regions within the amygdaloid complex. (Courtesy of Joel Price.)

(C)


Orbital and medial prefrontal cortex
Amygdala (basal-lateral nuclei)
Ventral basal ganglia
Mediodorsal nucleus of the thalamus

(C) The amygdala (specifically, the basal-lateral group of nuclei) participates in a "triangular" circuit linking the amygdala, the thalamic mediodorsal nucleus (directly and indirectly via the ventral parts of the basal ganglia), and the orbital and medial prefrontal cortex. These complex interconnections allow direct interactions between the amygdala and prefrontal cortex, as well as indirect modulation via the circuitry of the ventral basal ganglia.

sensory, visceral sensory, gustatory, and olfactory stimuli. Moreover, highly complex stimuli are often required to evoke a neuronal response. For example, there are neurons in the basal-lateral group of nuclei that respond selectively to the sight of faces, very much like the "face" neurons in the inferior temporal cortex (see Chapter 25).

In addition to sensory inputs, the prefrontal and temporal cortical connections of the amygdala give it access to more overtly cognitive neocortical circuits, which integrate the emotional significance of sensory stimuli and guide complex behavior.

Finally, projections from the amygdala to the hypothalamus and brainstem (and possibly as far as the spinal cord) allow it to play an important role in the expression of emotional behavior by influencing activity in both the somatic and visceral motor efferent systems.

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virtually anything in their environment; most importantly, they showed marked changes in emotional behavior. Because they had been caught in the wild, the monkeys had typically reacted with hostility and fear to humans before their surgery. Postoperatively, however, they were virtually tame. Motor and vocal reactions generally associated with anger or fear were no longer elicited by the approach of humans, and the animals showed little or no excitement when the experimenters handled them. Nor did they show fear when presented with a snake—a strongly aversive stimulus for a normal rhesus monkey. Klüver and Bucy concluded that this remarkable change in behavior was at least partly due to the interruption of the pathways described by Papez. A similar syndrome has been described in humans who have suffered bilateral damage of the temporal lobes.

When it was later demonstrated that the emotional disturbances of the Klüver–Bucy syndrome could be elicited by removal of the amygdala alone, attention turned more specifically to the role of this structure in the control of emotional behavior.

The Importance of the Amygdala

Experiments first performed in the late 1950s by John Downer at University College London vividly demonstrated the importance of the amygdala in aggressive behavior. Downer removed one amygdala in rhesus monkeys, at

Box C

The Reasoning Behind an Important Discovery*

Paul Bucy explains why he and Heinrich Klüver removed the temporal lobes in monkeys:

> When we started out, we were not trying to find out what removal of the temporal lobe would do, or what changes in behavior of the monkeys it would produce. What we found out was completely unexpected! Heinrich had been experimenting with mescaline. He had even taken it himself and had experienced hallucinations. He had written a book about mescaline and its effects. Later Heinrich gave mescaline to his monkeys. He gave everything to his monkeys, even his lunch! He noticed that the monkeys acted as though they experienced paraesthesias in their lips. They licked, bit and chewed their lips. So he came to me and said, "Maybe we can find out where mescaline has its actions in the brain." So I said, "OK."

We began by doing a sensory denervation of the face, but that didn't make any difference to the mescaline-induced behavior. So we tried motor denervation. That didn't make any difference, either. Then we had to sit back and think hard about where to look. I said to Heinrich, "This business of licking and chewing the lips is not unlike what you see in cases of temporal lobe epilepsy. Patients chew and smack their lips inordinately. So, let's take out the uncus." Well, we could just as well take out the whole temporal lobe, including the uncus. So we did.

We were especially fortunate with our first animal. This was an older female.… She had become vicious—absolutely nasty. She was the most vicious animal you ever saw; it was dangerous to go near her. If she didn't hurt you, she would at least tear your clothing. She was the first animal on which we operated. I removed one temporal lobe.… The next morning my phone was ringing like mad. It was Heinrich, who asked, "Paul, what did you do to my monkey? She is tame!" Subsequently, in operating on non-vicious animals, the taming effect was never so obvious.

That stimulated our getting the other temporal lobe out as soon as we could evaluate her. When we removed the other temporal lobe, the whole syndrome blossomed.

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*Excerpt from an interview of Bucy by K. E. Livingston in 1981. K. E. Livingston (1986) Epilogue: Reflections on James Wenceslas Papez, According to Four of his Colleagues. In *The Limbic System: Functional Organization and Clinical Disorders*. B. K. Doane and K. E. Livingston (eds.). New York: Raven Press.

the same time transecting the optic chiasm and the commissures that link the two hemispheres (principally, the corpus callosum and anterior commissure; see Chapter 26). In so doing, he produced animals with a single amygdala that had access only to visual inputs from the eye on the same side of the head. Downer found that the animals' behavior depended on which eye was used to view the world. When the monkeys were allowed to see with the eye on the side of amygdala lesion, they behaved in some respects like those described by Klüver and Bucy; for example, they were relatively placid in the presence of humans. If, however, they were allowed to see only with the eye on the side of the intact amygdala, they reverted to their normal fearful and often aggressive behavior. Thus, in the absence of the amygdala, a monkey does not interpret the significance of the visual stimulus presented by an approaching human in the same way as a normal animal. Importantly, only visual stimuli presented to the eye on the side of the ablation produced this abnormal state; thus if the animal was touched on either side, a full aggressive reaction occurred, implying that somatic sensory information about both sides of the body had access to the remaining amygdala. These anecdotal data, taken together with what is now a rich trove of empirical results and clinical observations in both experimental animals and humans show that the amygdala mediates neural processes that invest sensory experience with emotional significance.

To better understand the role of the amygdala in evaluating stimuli, and to define more precisely the specific circuits and mechanisms involved, several other animal models of emotional behavior have since been developed. One of the most useful is based on conditioned fear responses in rats. Conditioned fear develops when an initially neutral stimulus is repeatedly paired with an inherently aversive one. Over time, the animal begins to respond to the neutral stimulus with behaviors similar to those elicited by the threatening stimulus (i.e., it learns to attach a new meaning to the neutral stimulus). Studies of the parts of the brain involved in the development of conditioned fear in rats have begun to shed some light on this process. Joseph LeDoux and his colleagues at New York University trained rats to associate a tone with a mildly aversive foot shock delivered shortly after onset of the sound. To assess the animals' responses, they measured blood pressure and the length of time the animals crouched without moving (a fearful reaction called "freezing"). Before training, the rats did not react to the tone, nor did their blood pressure change when the tone was presented. After training, however, the onset of the tone caused a marked increase in blood pressure and prolonged periods of behavioral freezing. Using this paradigm, LeDoux and his collegues worked out the neural circuitry that established the association between the tone and fear (Figure 28.5). First, they demonstrated that the medial geniculate nucleus is necessary for the development of the conditioned fear response. This result is not surprising, since all auditory information that reaches the forebrain travels through the medial geniculate nucleus of the dorsal thalamus (see Chapter 12). They went on to show, however, that the responses were still elicited if the connections between the medial geniculate and auditory cortex were severed, leaving only a direct projection between the medial geniculate and the basal-lateral group of nuclei in the amygdala. Furthermore, if the part of the medial geniculate that projects to the amygdala was also destroyed, the fear

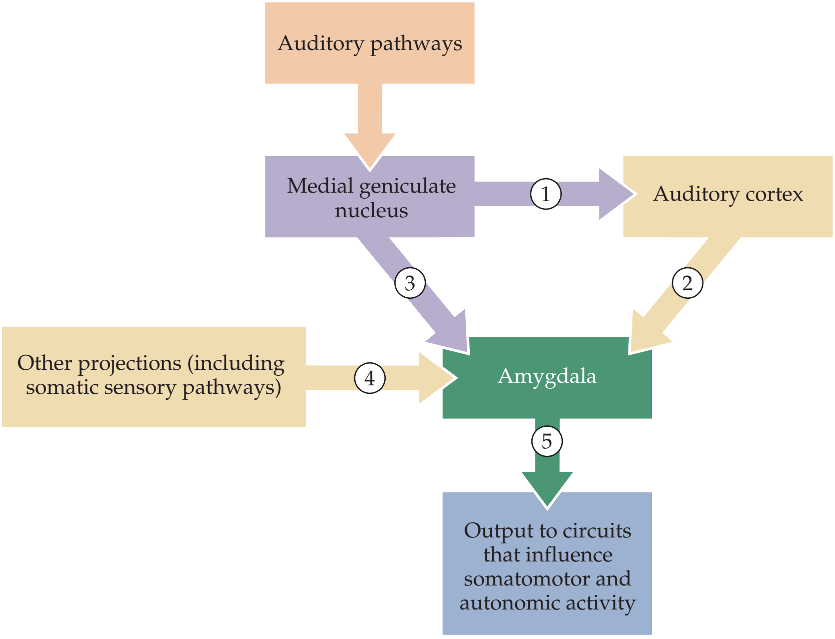

Auditory pathways
Medial geniculate nucleus
①
Auditory cortex
③
②
Other projections (including somatic sensory pathways)
④
Amygdala
⑤
Output to circuits that influence somatomotor and autonomic activity

Figure 28.5 Pathways in the rat brain that mediate the association of auditory and aversive somatic sensory stimuli. Information processed by the auditory centers in the brainstem is relayed to the auditory cortex via the medial geniculate nucleus (1). The amygdala receives auditory information indirectly via the auditory cortex (2) and directly from one subdivision of the medial geniculate (3). The amygdala also receives sensory information about other sensory modalities, including pain (4). Thus, the amygdala is in a position to associate diverse sensory inputs, leading to new behavioral and autonomic responses to stimuli that were previously devoid of emotional content (5).

responses were abolished. Subsequent work in LeDoux's laboratory established that projections from the central group of nuclei in the amygdala to the midbrain reticular formation are critical in the expression of freezing behavior, while other projections from this group to the hypothalamus control the rise in blood pressure.

Since the amygdala is a site where neural activity produced by both tones and shocks can be processed, it is reasonable to suppose that the amygdala is also the site where learning about fearful stimuli occurs. These results, among others, have led to the broader hypothesis that the amygdala participates in establishing associations between neutral sensory stimuli, such as a mild auditory tone or the sight of inanimate object in the environment, and other stimuli that have some primary reinforcement value (Figure 28.6). The neutral sensory input can be stimuli in the external environment, stimuli

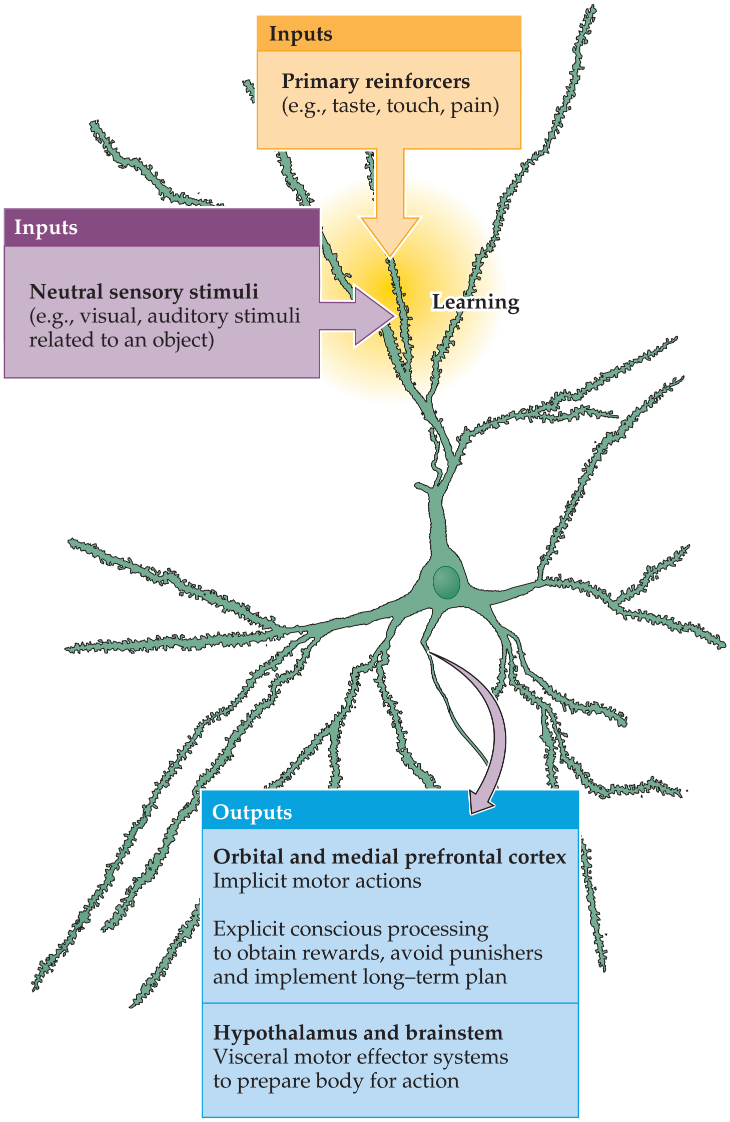

Inputs
Primary reinforcers
(e.g., taste, touch, pain)
Inputs
Neutral sensory stimuli
(e.g., visual, auditory stimuli
related to an object)
Learning
Outputs
Orbital and medial prefrontal cortex
Implicit motor actions
Explicit conscious processing
to obtain rewards, avoid punishers
and implement long–term plan
Hypothalamus and brainstem
Visceral motor effector systems
to prepare body for action

Figure 28.6 Model of associative learning in the amygdala relevant to emotional function. Most neutral sensory inputs are relayed to principal neurons in the amygdala by projections from "higher order" sensory processing areas that represent objects (e.g., faces). If these sensory inputs depolarize amygdalar neurons at the same time as inputs that represent other sensations with primary reinforcing value, then associative learning occurs by strengthening synaptic linkages between the previously neutral inputs and the neurons of the amygdala (see Chapter 24 for synaptic mechanisms of learning). The output of the amygdala then informs a variety of integrative centers responsible for the somatic and visceral motor expression of emotion, and for modifying behavior relevant to seeking rewards and avoiding punishment. (After Rolls, 1999.)

communicated centrally via the special sensory afferent systems, or internal stimuli derived from activation of visceral sensory receptors. The stimuli with primary reinforcement value include sensory stimuli that are inherently rewarding, such as the sight, smell, and taste of food, or stimuli with negative valences such as an aversive taste, loud sounds, or painful mechanical stimulation. The associative learning process itself is probably a Hebbian-like mechanism (see Chapters 23 and 24) that strengthens the connections relaying the information about the neutral stimulus, provided that they activate the postsynaptic neurons in the amygdala at the same time as inputs pertaining to the primary reinforcer. The discovery that long-term potentiation (LTP) occurs in the amygdala provides further support for this hypothesis. Indeed, the acquisition of conditioned fear in rats is blocked by infusion into the amygdala of NMDA antagonists, which prevents the induction of LTP. Finally, the behavior of patients with selective damage to the anterior-medial temporal lobe indicates that the amygdala plays a similar role in the human experience of fear (Box D).

The Relationship between Neocortex and Amygdala

As these observations on the limbic system (and the amygdala in particular) make plain, understanding the neural basis of emotions also requires understanding the role of the cerebral cortex. In animals like the rat, most behavioral responses are highly stereotyped. In more complex brains, however, individual experience is increasingly influential in determining responses to special and even idiosyncratic stimuli. Thus in humans, a stimulus that evokes fear or sadness in one person may have little or no effect on the emotions of another. Although the pathways underlying such responses are not well understood, the amygdala and its interconnections with an array of neocortical areas in the prefrontal cortex and anterior temporal lobe, as well as several subcortical structures, appear to be especially important in the higher order processing of emotion. In addition to its connections with the hypothalamus and brainstem centers that regulate visceral motor function, the amygdala has significant connections with several cortical areas in the orbital and medial aspects of the frontal lobe (see Box B). These cortical fields associate information from every sensory modality (including information about visceral activities) and can thus integrate a variety of inputs pertinent to moment-to-moment experience. In addition, the amygdala projects to the thalamus (specifically, the mediodorsal nucleus), which projects in turn to these same cortical areas. Finally, the amygdala innervates neurons in the ventral portions of the basal ganglia that receive the major cortico-striatal projections from the regions of the prefrontal cortex thought to process emotions. Considering all these seemingly arcane anatomical connections, the amygdala emerges as a nodal point in a network that links together the cortical (and subcortical) brain regions involved in emotional processing.

Clinical evidence concerning the significance of this circuitry linked through the amygdala has come from functional imaging studies of patients suffering from depression (Box E), in which this set of interrelated forebrain structures displays abnormal patterns of cerebral blood flow, especially in the left hemisphere. More generally, the amygdala and its connections to the prefrontal cortex and basal ganglia are likely to influence the selection and initiation of behaviors aimed at obtaining rewards and avoiding punishments (recall that the process of motor program selection and initiation is an important function of basal ganglia circuitry; see Chapter 17). The parts of

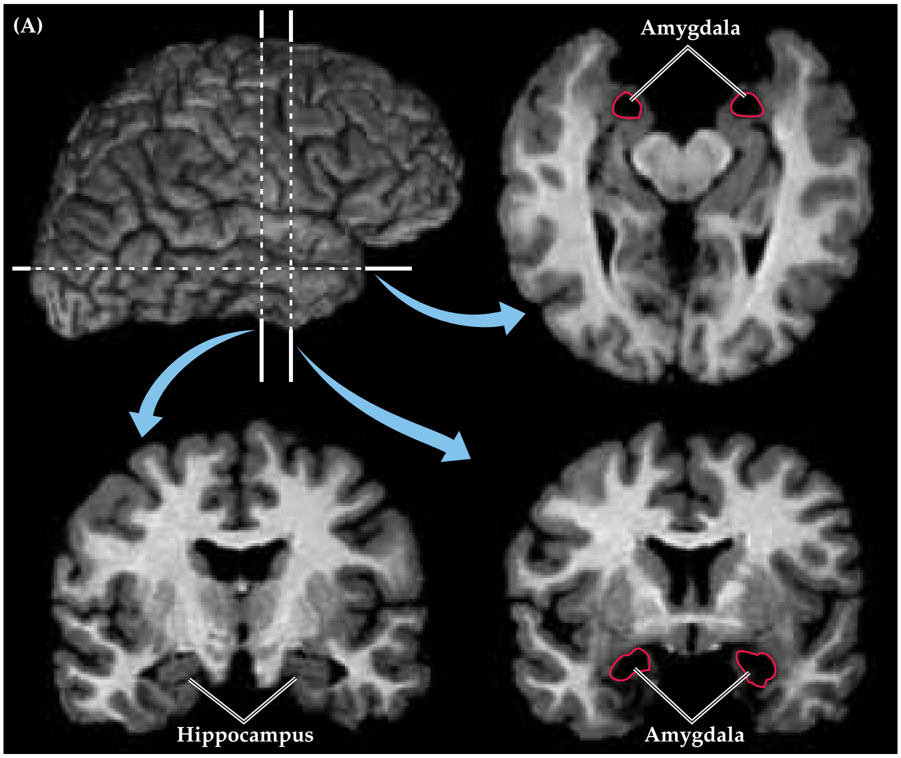
Box D

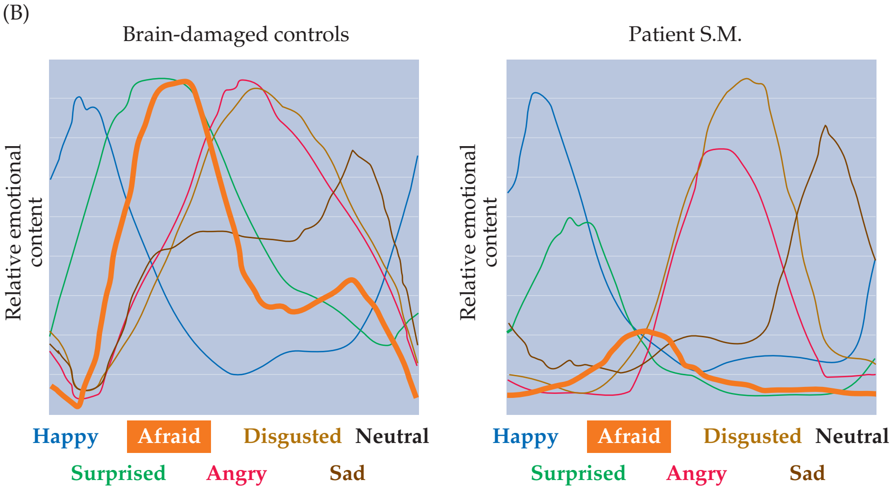
Fear and the Human Amygdala: A Case Study

Studies of fear conditioning in rodents show that the amygdala plays a critical role in the association of an innocuous auditory tone with an aversive mechanical sensation. Does this finding imply that the human amygdala is similarly involved in the experience of fear and the expression of fearful behavior? Recent reports of at least one extraordinary patient support the idea that the amygdala is indeed a key brain center for the experience of fear.

The patient (S.M.) suffers from a rare, autosomal recessive condition called Urbach-Wiethe disease, a disorder that causes bilateral calcification and atrophy of the anterior-medial temporal lobes. As a result, both of S.M.'s amygdalas are extensively damaged, with little or no detectable injury to the hippocampal formation or nearby temporal neocortex (Figure A). She has no motor or sensory impairment, and no notable deficits in intelligence, memory, or language function. However, when asked to rate the intensity of emotion in a series of photographs of facial expressions, she cannot recognize the emotion of fear (Figure B). Indeed, S.M.'s ratings of emotional content in fearful facial expressions were several standard deviations below the ratings of control patients who had suffered brain damage outside of the anterior-medial temporal lobe.

The investigators next asked S.M. (and the brain-damaged control subjects) to draw facial expressions of the same set of emotions from memory. Although the subjects obviously differed in artistic abilities and the detail of their renderings, S.M. (who has some artistic experience) produced skillful pictures of each emotion, except for fear (Figure C). At first, she could not produce a sketch of a fearful expression and, when prodded to do so, explained that "she did not know what an afraid





(A) MRI showing the extent of brain damage in patient S.M; note the bialateral destruction of the amygdala and the preservation of the hippocampus. (B) Patients with brain damage outside of the anterior-medial temporal lobe and patient S.M. rated the emotional content of a series of facial expressions. Each colored line represents the intensity of the emotions judged in the face. S.M. recognized happiness, surprise, anger, disgust, sadness, and neutral qualities in facial expressions about as well as controls. However, she failed to recognize fear (orange lines). (A courtesy of R. Adolphs.)

face would look like.” After several failed attempts, she produced the sketch of a cowering figure with hair standing on end, evidently because she knew these clichés about the expression of fear. In short, S.M. has a severely limited concept of fear and, consequently, fails to recognize the emotion of fear in facial expressions. Studies of other individuals with bilateral destruction of the amygdala are consistent with this account. As might be expected, S.M.’s deficiency also limits her ability to experience fear in situations where this emotion is appropriate.

Despite the adage “have no fear,” to truly live without fear is to be deprived of a crucial neural mechanism that facilitates appropriate social behavior, helps make advantageous decisions in critical circumstances, and, ultimately, promotes survival.

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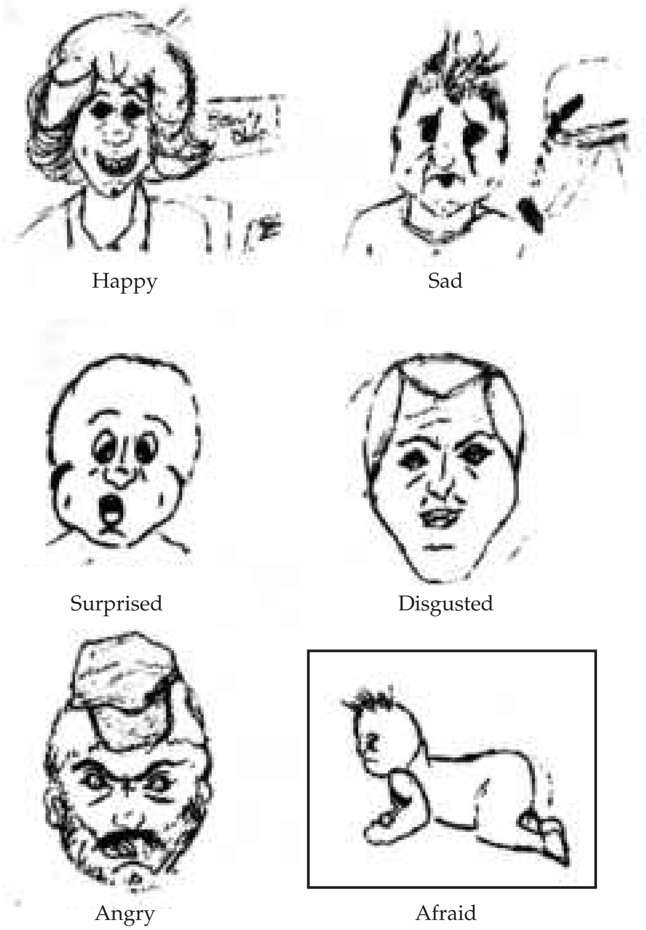
(C)



Happy

Sad

Surprised

Disgusted

Angry

Afraid

(C) Sketches made by S.M. when asked to draw facial expressions of emotion.

the prefrontal cortex interconnected with the amygdala are also involved in organizing and planning future behaviors; thus, the amygdala may provide emotional input to overt (and covert) deliberations of this sort (see the later section on “Emotion, Reason, and Social Behavior”).

Finally, it is likely that interactions between the amygdala, the neocortex and related subcortical circuits account for what is perhaps the most enigmatic aspect of emotional experience: the highly subjective “feelings” that attend most emotional states. Although the neurobiology of such experience is not understood, it is reasonable to assume that emotional feelings arise as a consequence of a more general cognitive capacity for self-awareness. In this conception, feelings entail both the immediate conscious experience of implicit emotional processing (arising from amygdala–neocortical circuitry) and explicit processing of semantically based thought (arising from hippocampal–neocortical circuitry; see Chapter 30). Thus, feelings are plausibly

Box E
Affective Disorders

Although some degree of disordered emotion is present in virtually all psychiatric problems, in affective (mood) disorders the essence of the disease is an abnormal regulation of the feelings of sadness and happiness. The most severe of these afflictions are major depression and manic depression. (Manic depression is also called "bipolar disorder," since such patients experience alternating episodes of depression and euphoria.) Depression, the most common of the major psychiatric disorders, has a lifetime incidence of 10–25% in women and 5–12% in men. For clinical purposes, depression (as distinct from bereavement or neurotic unhappiness) is defined by a set of standard criteria. In addition to an abnormal sense of sadness, despair, and bleak feelings about the future (depression itself), these criteria include disordered eating and weight control, disordered sleeping (insomnia or hypersomnia), poor concentration, inappropriate guilt, and diminished sexual interest. The personally overwhelming quality of major depression has been compellingly described by patient/authors such as William Styron, and by afflicted psychologists such as Kay Jamison. The depressed patient's profound sense of despair has been nowhere better expressed than by Abraham Lincoln, who during a period of depression wrote:

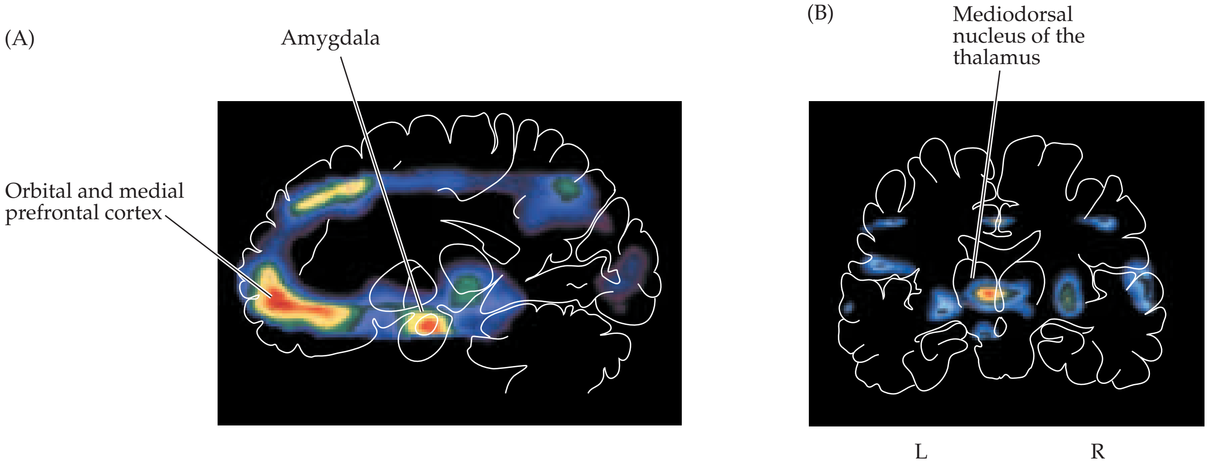
> I am now the most miserable man living. If what I feel were equally distributed to the whole human family, there would not be one cheerful face on earth. Whether I shall ever be better, I cannot tell; I awfully forebode I shall not. To remain as I am is impossible. I must die or be better, it appears to me.

Indeed, about half the suicides in this country occur in individuals with clinical depression.

Not many decades ago, depression and mania were considered disorders that arose from circumstances or a neurotic inability to cope. It is now universally accepted that these conditions are neurobiological disorders. Among the strongest lines of evidence for this consensus are studies of the inheritance of these diseases. For example, the concordance of affective disorders is high in monozygotic compared to dizygotic twins. It has also become possible to study the brain activity of patients suffering from affective disorders by noninvasive brain imaging (see Figure). In at least one condition, unipolar depression, abnormal patterns of blood flow are apparent in the "triangular" circuit interconnecting the amygdala, the mediodorsal nucleus of the thalamus, and the orbital and medial prefrontal cortex (see Box B). Of particular interest is the significant correlation of abnormal blood flow in the amygdala and the clinical severity of depression, as well as the observation that the abnormal blood flow pattern in the prefrontal cortex returns to normal when the depression has abated.

Despite evidence for a genetic predisposition and an increasing understanding of the brain areas involved, the cause of these conditions remains unknown. The efficacy of a large number of drugs

Areas of increased blood flow in the left amygdala, orbital, and medial prefrontal cortex (A) and in a location in the left medial thalamus consistent with the mediodorsal nucleus (B) from a sample of patients diagnosed with unipolar clinical depression. The "hot" colors indicate statistically significant increases in blood flow, compared to a sample of nondepressed subjects. (From Drevets and Raichle, 1994.)


(A)
Amygdala
Orbital and medial prefrontal cortex
(B)
Mediodorsal nucleus of the thalamus
L
R

that influence catecholaminergic and serotonergic neurotransmission strongly implies that the basis of the disease(s) is ultimately neurochemical (see Figure 6.12 for an overview of the projections of these neural systems). The majority of patients (about 70%) can be effectively treated with one of a variety of drugs (including tricyclic antidepressants, monoamine oxidase inhibitors, and selective serotonin reuptake inhibitors). Most successful are drugs that selectively block the uptake of serotonin without affecting the uptake of other neurotransmitters; these drugs are commonly known as selective serotonin reuptake inhibitors, or SSRIs. Three such inhibitors—fluoxetine (Prozac®), sertraline (Zoloft®), and paroxetine (Paxil®)—are especially effective in treating depression and have few of the side effects of the older, less specific drugs. Perhaps the best indicator of the success of these drugs has been their wide acceptance: although the first SSRI's were approved for clinical use only in the late 1980s, they are now among the most prescribed pharmaceuticals.

Most depressed patients who use drugs such as the SSRI's report that they lead fuller lives and are more energetic and organized. Based on such information, these drugs are sometimes used not only to combat depression but also to "treat" individuals who have no definable psychiatric disorder. This abuse raises important social questions, similar to those posed by Aldous Huxley in his 1932 novel, where the mythical drug "Soma" was routinely administered to the inhabitants of his fictitious *Brave New World* to keep them content and docile. Presumably there is a middle ground between excessive suffering and excessive tranquility.

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conceived as the product of an emotional working memory that sustains neural activity related to the processing of these various elements of emotional experience. Given the evidence for working memory functions in the prefrontal cortex (see Chapter 25), this portion of the frontal lobe—especially the orbital and medial sector—is the likely neural substrate where such associations are maintained in conscious awareness (Figure 28.7).

Cortical Lateralization of Emotional Functions

Since functional asymmetries of complex cortical processes are commonplace (see Chapters 25 and 26), it should come as no surprise that the two hemispheres make different contributions to the governance of emotion.

Emotionality is lateralized in the cerebral hemispheres in at least two ways. First, as discussed in Chapter 26, the right hemisphere is especially important for the expression and comprehension of the affective aspects of speech. Thus, patients with damage to the supra-Sylvian portions of the posterior frontal and anterior parietal lobes on the right side may lose the ability

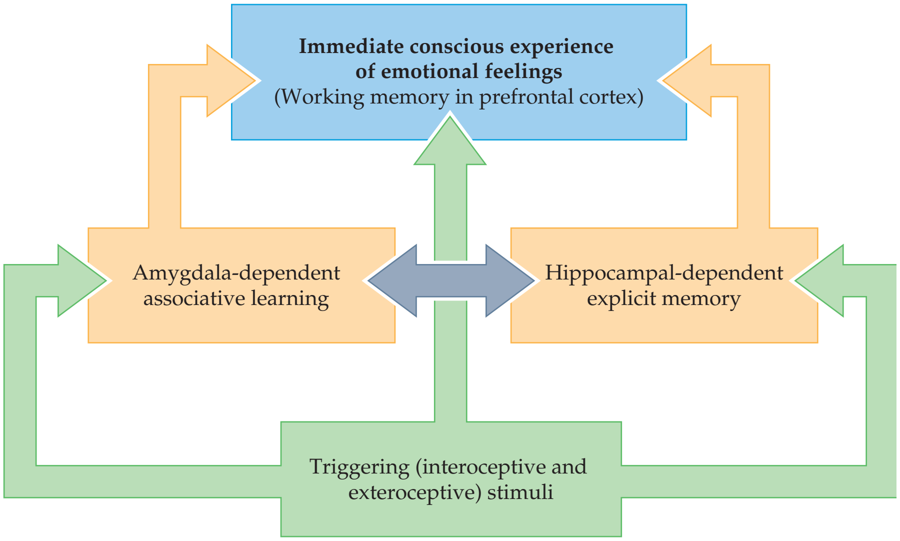
Immediate conscious experience of emotional feelings
(Working memory in prefrontal cortex)
Amygdala-dependent associative learning
Hippocampal-dependent explicit memory
Triggering (interoceptive and exteroceptive) stimuli

Figure 28.7 Neural model for the awareness of emotional feelings. The highly subjective feelings associated with emotional experience presumably arise from neural systems in the prefrontal cortex that produce awareness of emotional processing. (After LeDoux, 2000.)

to express emotion by modulation of their speech patterns (recall that this loss of emotional expression is referred to as *aprosody* or *aprosodia*, and that similar lesions in the left hemisphere give rise to Broca's aphasia). Patients with aprosodia tend to speak in a monotone, no matter what the circumstances or meaning of what is said. For example, one such patient, a teacher, had trouble maintaining discipline in the classroom. Because her pupils (and even her own children) couldn't tell when she was angry or upset, she had to resort to adding phrases such as "I am angry and I really mean it" to indicate the emotional significance of her remarks. The wife of another patient felt her husband no longer loved her because he could not imbue his speech with cheerfulness or affection. Although such patients cannot express emotion in speech, they nonetheless experience normal emotional feelings.

A second way in which the hemispheric processing of emotionality is asymmetrical concerns mood. Both clinical and experimental studies indicate that the left hemisphere is more importantly involved with what can be thought of as positive emotions, whereas the right hemisphere is more involved with negative ones. For example, the incidence and severity of depression (see Box E) is significantly higher in patients with lesions of the left anterior hemisphere compared to any other location. In contrast, patients with lesions of the right anterior hemisphere are often described as unduly cheerful. These observations suggest that lesions in the left hemisphere result in a relative loss of positive feelings, facilitating depression, whereas lesions of the right hemisphere result in a loss of negative feelings, leading to inappropriate optimism.

Hemispheric asymmetry related to emotion is also apparent in normal individuals. For instance, auditory experiments that introduce sound into one ear or the other indicate a right-hemisphere superiority in detecting the emotional nuances in speech. Moreover, when facial expressions are specifi-

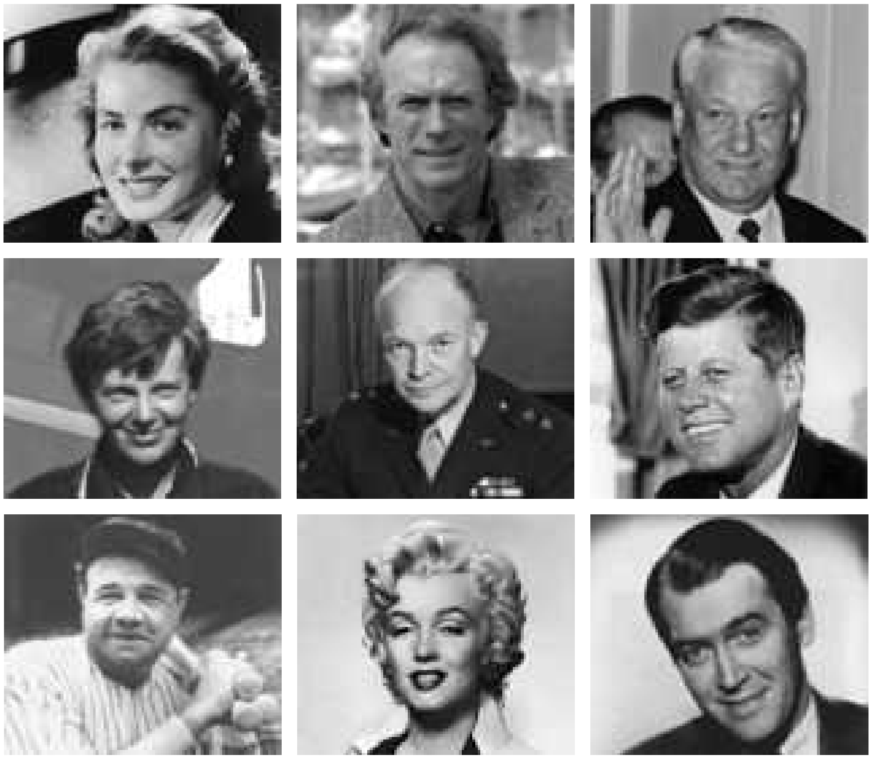

Figure 28.8 Asymmetrical smiles on some famous faces. Studies of normal subjects show that facial expressions are often more quickly and fully expressed by the left facial musculature than the right, as suggested by examination of these examples (try covering one side of the faces and then the other). Since the left lower face is governed by the right hemisphere, some psychologists have suggested that the majority of humans are "left-faced," in the same general sense that most of us are right-handed. (After Moscovitch and Olds, 1982; images from Microsoft® Encarta Encyclopedia 98.)

cally presented to either the right or the left visual hemifield, the depicted emotions are more readily and accurately identified from the information in the left hemifield (that is, the hemifield perceived by the right hemisphere; see Chapters 11 and 26). Finally, kinematic studies of facial expressions show that most individuals more quickly and fully express emotions with the left facial musculature than with the right (recall that the left lower face is controlled by the right hemisphere, and vice versa) (Figure 28.8). Taken together, this evidence is consistent with the idea that the right hemisphere is more intimately concerned with both the perception and expression of emotions than is the left hemisphere. However, it is important to remember that, as in the case of other lateralized behaviors (language, for instance), both hemispheres participate in processing emotion.

Emotion, Reason, and Social Behavior

The experience of emotion—even on a subconscious level—has a powerful influence on other complex brain functions, including the neural faculties responsible for making rational decisions and the interpersonal judgments that guide social behavior. Evidence for this statement has come principally from studies of patients with damage to parts of the orbital and medial prefrontal cortex, as well as patients with injury or disease involving the amygdala (see Box D). Such patients often have impairments in emotional processing, especially of the emotions engendered by complex personal and social situations, and they have difficulty making advantageous decisions (see also Chapter 25). Adding to this body of evidence are results from brain imaging studies in normal subjects in which investigators have mapped the brain structures that participate in the necessary emotional and social appraisals.

Antonio Damasio and his colleagues at the University of Iowa have suggested that such decision-making entails the rapid evaluation of a set of possible outcomes with respect to the future consequences associated with each course of action. It seems plausible that the generation of conscious or subconscious mental images that represent the consequences of each contingency triggers emotional states that involve either actual alterations of somatic and visceral motor function, or the activation of neural representations of such activity. Whereas William James proposed that we are "afraid because we tremble," Damasio and his colleagues suggest a vicarious representation of motor action and sensory feedback in the neural circuits of the frontal and parietal lobes. It is these vicarious states, according to Damasio, that give mental representations of contingencies the emotional valence that helps an individual to identify favorable or unfavorable outcomes.

Experimental studies of fear conditioning have implied just such a role for the amygdala in associating sensory stimuli with aversive consequences. For example, the patient described in Box D showed an impaired ability to recognize and experience fear, together with impairment in rational decision-making. Similar evidence of the emotional influences on decision-making have also come from studies of patients with lesions in the orbital and medial prefrontal cortex. These clinical observations suggest that the amygdala and prefrontal cortex, as well as their striatal and thalamic connections, are not only involved in processing emotions, but also participate in the complex neural processing responsible for rational thinking. These same neural networks are engaged by sensory stimuli (e.g., facial expressions) that convey important cues pertinent to appraising social circumstances and conventions. Thus, when judging the trustworthiness of human faces—a task of considerable importance for successful interpersonal relations—neural activity in the amygdala is specifically increased, especially when the face in question is deemed untrustworthy (Figure 28.9). It is not surprising, then, that subjects with bilateral damage to the amygdala differ from control subjects in their appraisals of trustworthiness; indeed, individuals with such impairments often show inappropriately friendly behavior toward strangers in real-life social situations. Such evidence adds further weight to the idea that emotional processing is crucial for competent performance in a wide variety of complex brain functions.

Summary

The word "emotion" covers a wide range of states that have in common the association of visceral motor responses, somatic behavior, and powerful subjective feelings. The visceral motor responses are mediated by the visceral motor nervous system, which is itself regulated by inputs from many other parts of the brain. The organization of the somatic motor behavior associated with emotion is governed by circuits in the limbic system, which includes

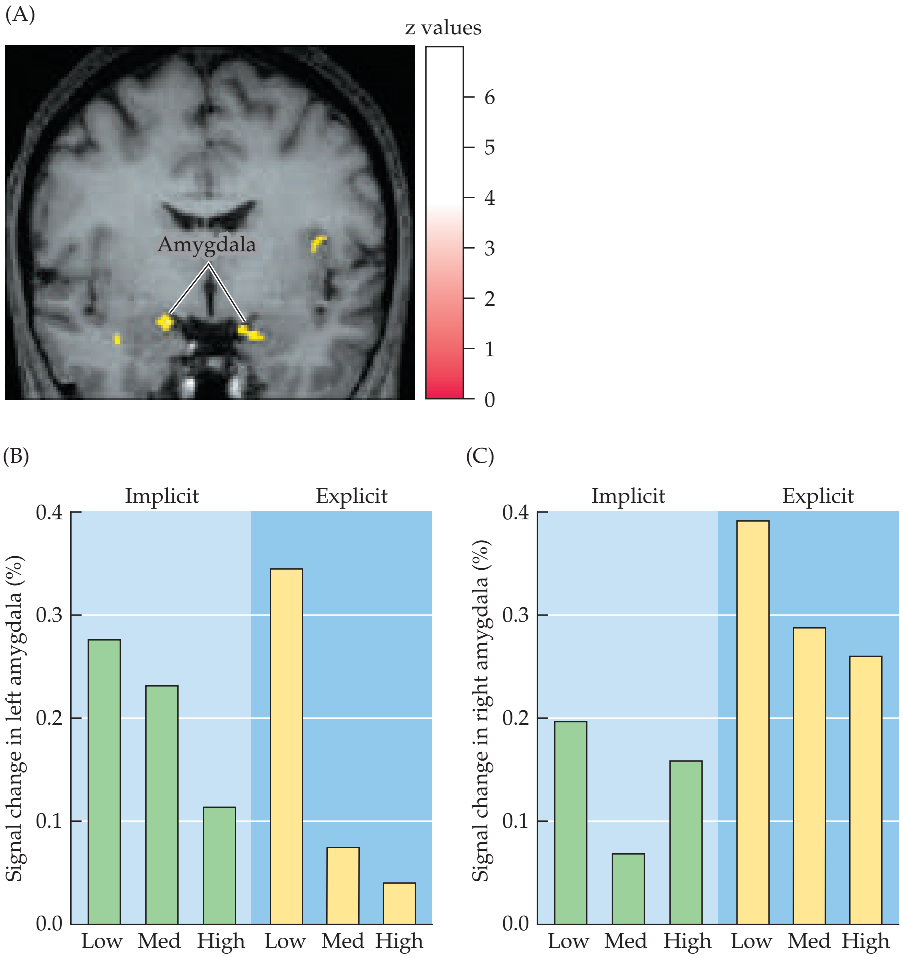

Figure 28.9 Activation of the amygdala during judgments of trustworthiness. (A) Functional MRI shows increased neural activation bilaterally in the amygdala when normal subjects appraise the trustworthiness of human faces; activity is also increased in the right insular cortex. (B, C) The degree of activation is greatest when subjects evaluate faces that are considered untrustworthy (Low, Med and High indicate ratings of trustworthiness; Low = untrustworthy). The same effect was observed when subjects were instructed to evaluate the trustworthiness of the faces (explicit condition) or whether the faces were those of high school or university students (implicit condition). (After Winston et al., 2002; A courtesy of J. Winston.)

the hypothalamus, the amygdala, and several regions of the cerebral cortex. Although a good deal is known about the neuroanatomy and transmitter chemistry of the different parts of the limbic system, there is still a dearth of information about how this complex circuitry mediates specific emotional states. Similarly, neuropsychologists, neurologists and psychiatrists are only now coming to appreciate the important role of emotional processing in other complex brain functions, such as decision-making and social behavior. A variety of other evidence indicates that the two hemispheres are differently specialized for the governance of emotion, the right hemisphere being the more important in this regard. The prevalence and social significance of human emotions and their disorders ensure that the neurobiology of emotion will be an increasingly important theme in modern neuroscience.

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Chapter 29

Sex, Sexuality, and the Brain

Overview

"Vive la difference." "Isn't that just like a (wo)man?" "It's on the Y chromosome." These expressions denote pleasure (or displeasure) with phenotypic sexual differences—how females and males look and behave. Sex-related differences in the phenotypic expression of genotype are called sexual dimorphisms. While some of the behavioral distinctions involved may be rooted in cultural or social norms, sexual dimorphisms arise primarily because the brains of females and males are in some respects different. In the rat (the animal in which most experimental work has been done), several structures in female and male brains clearly differ in the number, size, and connectivity of their constituent neurons. In humans and other primates, structural differences are less obvious but nonetheless present. In both rats and humans, sexually dimorphic brain structures tend to cluster around the third ventricle in the anterior hypothalamus and are an integral part of the system that governs visceral motor behavior. Other sexual dimorphisms are apparent in cerebral cortical structures, implying differences in more complex regulatory and other behaviors. The development of these structural differences depends primarily on the early effect of gonadal steroid hormones on maturing brain circuits, an influence that apparently continues to some extent throughout life. The functional consequences of sexual dimorphisms in rodents are beginning to be well understood. Although the significance of such differences in humans is less clear, they provide a plausible neural basis for the wide variety of human sexual behavior.

Sexually Dimorphic Behavior

Many animal behaviors differ between the sexes and are therefore referred to as **sexually dimorphic** (*dimorphic* means having two forms). However, dimorphic behaviors and their neural substrates often overlap. Mounting behaviors in male and female rodents, for example, depend on social context and life history, as well as on hormones and the brain structures that produce them.

Some sexually dimorphic behaviors are simply part of the reproductive repertoire, whereas others are associated with cognitive functions. An example of dimorphic behavior related to reproduction is apparent in songbirds. In many species, the male produces complex song, but the female does not. Song production arises from the activity of specific brain nuclei; as described in Chapter 23, these nuclei are much larger in males than in females. The size of song control nuclei increases in females treated with testosterone or estradiol during development, and these "masculinized" females sing.

Rodents also exhibit sexually dimorphic behaviors associated with reproduction. Examples include the priming of the genitalia for sexual intercourse, and a stereotypical position assumed while having sex (typically *lordosis* for females and *mounting* for males).

Just as courting and behaviors associated with the sex act can be dimorphic, other more complex reproductive behaviors such as building nests, caring for the young, foraging for food, nursing, and so on can take different forms in female and male. In humans, the different behaviors of males and females can be far subtler, including sexual identity, the choice of a sexual partner, and behaviors that are not related directly to sexual or reproductive function, such as spatial thinking and use of language.

In humans, as in other animals, the full range of these behavioral differences is necessarily based on the details of the underlying neural circuitry. Accordingly, neurobiologists have long looked for differences between the brains of females and males that might explain sexually dimorphic behaviors. As described later in this chapter, they have found many examples. Differences in the nervous system, like the behavioral differences they give rise to, are also referred to as sexually dimorphic. Bear in mind, however, that whereas brain and behavioral differences in songbirds or rodents usually have two distinct forms, in human females and males these differences tend to vary along a continuum.

What Is Sex?

Human sexual behaviors are—quite obviously—less stereotyped than those of rodents. Like memory, language, sleep, and other higher order brain functions, sexual behavior (especially when its neurobiological underpinnings are considered) is by no means simple to sort out, or even to categorize.

Roughly speaking, the concept of sex can be subdivided into three categories: chromosomal sex, phenotypic sex, and gender. **Chromosomal sex** refers specifically to an individual's sex chromosomes. Most humans have either two X chromosomes or one X and one Y chromosome, with XX being a chromosomal female and XY a chromosomal male. **Phenotypic sex** refers to an individual's sex as determined by their internal and external genitalia, the expression of secondary sex characteristics, and their behavior. In the prototypical case, during development the XX genotype leads to an individual with ovaries, oviducts, uterus, cervix, clitoris, labia, and vagina—i.e., a phenotypic female. The XY genotype leads to a person with testicles, epididymis, vas deferens, seminal vesicles, penis, and scrotum—a phenotypic male (Box A).

Gender, as the term is most often used, refers to an individual's subjective perception of their sex and their sexual orientation, which is harder to define than chromosomal or phenotypic sex. It should also be apparent that some people consider gender to be a political and social construct. For present purposes, however, gender entails self-appraisal according to the traits most often associated with one sex or the other (called gender traits), which are influenced by societal expectations and cultural norms as well as by biology. Sexual orientation also entails self-appraisal in the context of culture. To understand the neurobiology of sex, it is helpful to think of chromosomal sex as largely immutable; phenotypic sex as modifiable by developmental processes, hormone treatments, and/or surgery; and gender as a more complex social and cultural construct that an individual may or may not want to accept.

Clearly, chromosomal sex, phenotypic sex, and gender will not always be aligned. Genetic variations in alignment can challenge the usual definitions of female and male, and for the affected individuals can lead to psychosocial conflicts, sexual dysfunction, and other problems. These variations include individuals who are chromosomally XO (Turner's syndrome), XXY (Klinefelter's syndrome), and XYY, with each of these genotypes having a particular phenotype. Other genetic variations entail mutations in genes coding for hormone receptors or for the hormones themselves. For instance in some XX individuals, a metabolic disorder called **congenital adrenal hyperplasia (CAH)** leads to overactive adrenals during maturation, resulting in abnormally high levels of circulating androgens and hence (along with severe salt imbalance), an ambiguous sexual phenotype. In addition to having a large clitoris and fused labia at birth, women with CAH often exhibit behavioral traits more often associated with boys than girls as children, and as adults they may be more likely to form homosexual relationships than are members of control groups. By analogy with the studies in rodents, high levels of circulating androgens may stimulate sexually dimorphic brain circuitry to have a male rather than female organization, leading to more aggressive play and the eventual choice of a female sexual partner.

An example of a mutation in a gene responsible for hormone receptors is **androgen insensitivity syndrome (AIS)**, also called **testicular feminization**. In an XY individual with AIS, the testes form and secrete testosterone and Müllerian-inhibiting hormone, as in normal males (see Box A). The deficiency of receptors for these androgens, however, leads to the development of female external genitalia in an individual who is chromosomally male. Thus, people with complete androgen insensitivity syndrome look like females and self-identify as female, even though they have a Y chromosome. Since they are generally not aware of their condition until puberty (when they fail to menstruate), such individuals see themselves as female and are experienced by the rest of society as female. As a result of the lack of androgen receptors, the gender identity of androgen-insensitive individuals matches their external sexual phenotype, but not their chromosomal sex. Androgen-insensitive individuals also present one of the strongest arguments that brain circuits in primates are masculinized primarily by the action of androgens (as opposed to the effects of estrogens, which are the masculinizing agent in rodents).

Another variation in the alignment of chromosomal sex, phenotype, and gender occurs in certain chromosomal males who are phenotypic females early in life, but whose sexual phenotype changes at puberty. As infants and children, the genitalia of these individuals resembles that of females more than of males because they lack an enzyme, 5-α-reductase, that promotes the early development of male genitalia (see Box A). Such children have labia with an enlarged clitoris; since their testes have not descended by birth, they are generally raised as females. At puberty, however, when the testicular secretion of androgen becomes high, the clitoris enlarges into a penis and the testes descend, changing these individuals into phenotypic males. In the Dominican Republic and Haiti, where this congenital syndrome has been thoroughly studied in a particular pedigree, the condition is referred to colloquially as "testes-at-twelve." Now that the condition is well recognized in areas where it is prevalent, the children in these pedigrees are raised with the understanding that their genitalia will change. But even if the situation goes unrecognized, such individuals generally change their gender identification at puberty, and most eventually assume a male role, for reasons that are further considered in Box B.

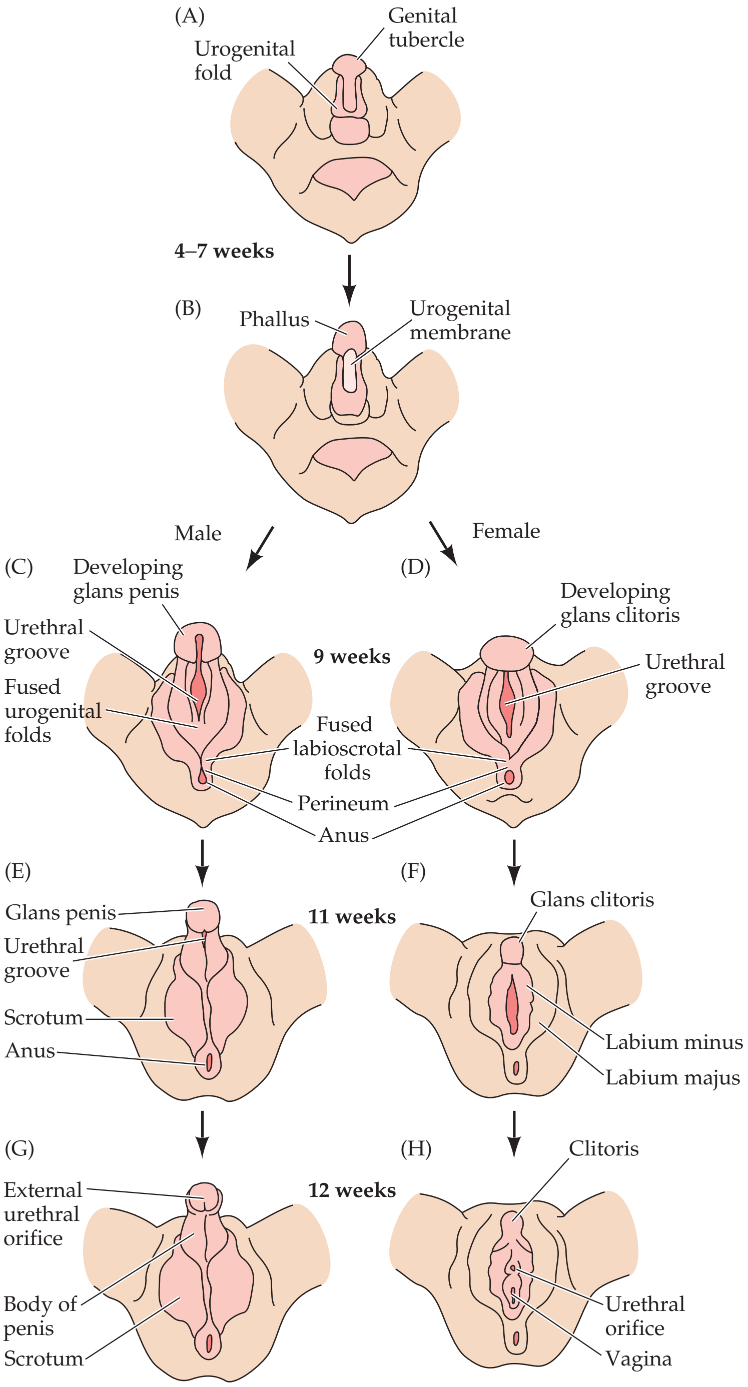
Box A

The Development of Male and Female Phenotypes

The presence of either two X chromosomes or an X and a Y chromosome in the cells of an embryo sets in motion events that establish phenotypical sex, including the sexually dimorphic development of the brain. The relevant neural effects are determined by the production of hormones, which depends in turn on the presence of either female or male gonads.

The early stages of human embryonic development follow a plan that produces common precursors for the gonads. By about the sixth week of gestation, the primordial gonads have formed from somatic mesenchyme tissue, near the developing kidneys. Cells in the gonads differentiate into supporting and hormone-producing cells; the **germline cells**, which divide by meiosis rather than mitosis and eventually become ova or sperm have a different origin, and migrate to the gonads from the yolk sac. Attached to the primordial gonads are two sets of tubes—the **Müllerian** and **Wolffian ducts**—that are the progenitors of the internal genitalia. Developing simultaneously is an undifferentiated structure called the **urogenital groove**, the progenitor of the external genitalia.

The primary genetic influence on the development of the typical male phenotype is the sex-determining region on the Y chromosome, the ***Sry* gene**. When this region of the chromosome is activated during development, it turns on the production of a protein called **testicular determining factor** (**TDF**). It is TDF that instructs the testes to begin developing. Once activated, the male primordial gonads begin to produce testosterone (elaborated by the Leydig cells). The cells of the testes also secrete **Müllerian-inhibiting hormone**, which prevents the Müllerian ducts from developing and allows the Wolffian ducts to develop into the epididymis, vas deferens, and semi-


(A)
Urogenital fold
Genital tubercle
4–7 weeks
(B)
Phallus
Urogenital membrane
Male
Female
(C)
Developing glans penis
Urethral groove
Fused urogenital folds
9 weeks
(D)
Developing glans clitoris
Urethral groove
Fused labioscrotal folds
Perineum
Anus
(E)
Glans penis
Urethral groove
Scrotum
Anus
11 weeks
(F)
Glans clitoris
Labium minus
Labium majus
(G)
External urethral orifice
Body of penis
Scrotum
12 weeks
(H)
Clitoris
Urethral orifice
Vagina

Development of human female and male external genitalia. (A, B) Indifferent stage, weeks 4–7 of gestation. (D, F, H) Differentiation in the female genitalia at weeks 9, 11, and 12, respectively. (C, E, G) Differentiation in the male genitalia at the same intervals. (After Moore, 1977.)

nal vesicles. Under these influences, the tissue around the urogenital groove becomes the penis and scrotum.

Androgens alone, however, are not sufficient for male differentiation. Ken Korach's group at the National Institute for Environmental Health Sciences has demonstrated that estrogens are also needed for the hormonal differentiation of the testes. More specifically, XY mice lacking estrogen receptors develop testes, but there is disruption of spermatogenesis and ultimately degeneration of the seminiferous tubules, leading to sterility. Thus the presence of TDF and the consequent production of androgens early in life lead to the differentiation of the male body and brain, but estrogens are also essential for the full development of the male phenotype.

In XX embryos, the absence of TDF, testosterone, and Müllerian-inhibiting hormone allows the indifferent gonad to differentiate into an ovary, the Wolffian ducts to degenerate, and the Müllerian ducts to develop into the oviducts, uterus, and cervix. The tissue around the urogenital groove becomes the clitoris, labia, and vagina. In short, the early absence of androgens leads to the differentiation of a female body and brain. However, development of the female phenotype also depends on estrogens; the absence of both α and β estrogen receptors results in ovaries that resemble testes, with structures resembling seminiferous tubule (including Sertoli-like cells) and the expression of Müllerian-inhibiting hormone.

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The general term used to describe all these variations is *intersexuality*. Intersexuality is apparent in 1 to 2% of all live births. In addition to the more clearly defined categories of Klinefelter's syndrome, Turner's syndrome, AIS, 5-α-reductase deficiency, and CAH, the many subtle permutations and combinations of genes, hormones, and environment clearly present a large number of biological and behavioral possibilities.

Hormonal Influences on Sexual Dimorphism

The development of sexual dimorphisms in the central nervous system is ultimately an outcome of chromosomal sex. Chromosomal combinations usually determine the phenotype of the gonads; the gonads, in turn, are responsible for producing most of the circulating sex hormones (see Box A). Differences in circulating hormones lead to a variety of differential effects on the individual's development, including their physical appearance, response to pharmacological treatments, susceptibility to certain diseases, and brain development.

The establishment of phenotypic dimorphisms under the influence of different relative amounts of circulating hormones has been best studied in rodents. This work has shown that different levels of hormones at critical times organizes and/or activates circuits generating female- or male-typical behavior. Males have an early surge of testosterone, which masculinizes the genitalia and nervous system, and ultimately behavior. Paradoxically, many of the effects of testosterone on the rodent brain are really due to estrogens

Box B
The Case of Bruce/Brenda

In the early 1960s, identical XY twins were born to a Canadian couple. When the twins were 7 months old, the parents had them circumcised. The surgeon, performing the operation using an electrocautery knife, burned one of the twins' penises so severely that the penis was, in essence, destroyed. The medical consensus conveyed to the parents by the local physicians was that the disfigured twin would be unable to have a normal heterosexual life, would be shunned by his peers, and would suffer in a variety of other ways. Given this dire prognosis, the parents consulted an eminent sex researcher, John Money at Johns Hopkins University, to help them decide what should be done.

After meeting with the family, Money advocated that they surgically reassign the child's sex and raise the boy as a girl. The parents consented, and at age 17 months the child's testes were removed and his scrotum reshaped to resemble a vulva. The little boy, Bruce, became known as Brenda within the family and personal circle; Money's medical records and published papers used the pseudonyms "John" and "Joan."

The parents did everything they could to raise Brenda as a normal female. Although Money's published reports were optimistic, subsequent interviews with the family, including the child himself, indicated that the truth was far more complex, and indeed deeply problematic. In a detailed follow-up of the case, Milton Diamond of the University of Hawaii and Keith Sigmundson described the struggle that Brenda suffered from the earliest age. The child refused to wear dresses, urinated standing up, always felt that something was wrong, and refused to comply with the hormone treatments that were initiated at puberty. At the age of 14, Brenda demanded to know the truth, and her equally frustrated parents reluctantly gave an account of the early events that had resulted in the current situation.

Ironically, Brenda was greatly relieved to understand why "she" had always been subject to such deeply conflicting feelings, which had sometimes made life so miserable that "she" contemplated suicide. Brenda immediately reverted to male dress and behavior and started going by the name of David. David, who is now nearly 40, eventually underwent surgery to be reconfigured as a phenotypic male. He married, adopted his wife's children, and has lived a relatively conventional life as a father and husband.

This case underscores the fact that, in the words of Diamond and Sigmundson, "the evidence [is] overwhelming that normal humans are not psychosocially neutral at birth but are, in keeping with their mammalian heritage, predisposed and biased to interact with environmental, familial, and social forces in either a male or female mode." Cases like David's raise serious moral and ethical questions about the assignment of gender when, for one reason or another, that option is open. Since there is no indication at birth how the brain has been shaped by early exposure to hormones, in many cases there is insufficient information to know with what sex the child, or the adult, will ultimately identify. In David's case, a grievous mistake was made by failing to understand the overwhelming influence on the brain of circulating androgens during early sexual development. David, whose surname is Reimer, is the subject of the biography by J. Colapinto listed below, and has welcomed the opportunity to make his case known in the interest of preventing such mistakes in the future.

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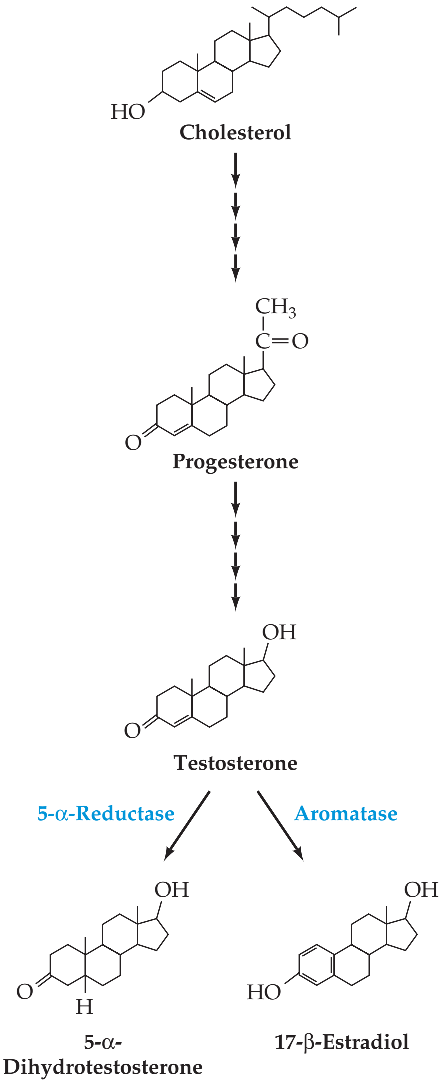
in the developmental window two weeks prenatal to two weeks postnatal: rodent neurons contain an enzyme (**aromatase**) that converts testosterone to **estradiol**, a form of estrogen. Thus, the surge of testosterone in developing males is effectively a surge of estradiol. Although testosterone is popularly considered the "male" hormone and estrogen the "female" hormone, the active agent in the brains of both male and female rodents is estradiol.

Once the conversion of testosterone to estradiol has occurred, estradiol can influence gene transcription by binding with intracellular receptors (α- and β-estrogen receptors) that regulate gene transcription (Figure 30.1). In

Figure 29.1 All sex steroids are synthesized from cholesterol. Cholesterol is first converted to progesterone, the common precursor, by four enzymatic reactions (represented by the four arrows). Progesterone can then be converted into testosterone via another series of enzymatic reactions; testosterone in turn is converted to 5-α-dihydrotestosterone via 5-α-reductase, or to 17-β-estradiol via an aromatase. 17-β-estradiol mediates most of the known hormonal effects in the brains of both female and male rodents.



mammals generally, fetuses are exposed to estrogens generated by the maternal ovary and placenta. Why doesn't this estrogen interfere with sexual differentiation in female offspring? Apparently, the answer is that developing mammals have a circulating protein called **α-fetoprotein** that binds circulating estrogens. The female brain is kept from early exposure to large amounts of estrogens, since estrogens are bound by α-fetoprotein; the male brain, however, *is* exposed via early testosterone surge; testosterone is not affected by α-fetoprotein, and is aromatized to estradiol only once inside neurons.

The conversion of testosterone to estrogen may not be as important in humans and other primates, where evidence suggests that sexual differentiation of the brain relies more on androgens and androgen receptors. It is also androgens that bear most of the responsibility for stimulating sex drive in females as well as males. For this reason, XY individuals with AIS can be "super-feminine" in their behavior and rarely choose females as sexual partners.

Finally, the influence of hormones in humans and other animals may be reinforced by sex differences established by genetic effects that are unrelated to hormonal differences during development. For example, Ingrid Reisert, working at the Universitat Albert-Einstein in Germany established that there are sex differences in the development of dopaminergic fibers in cell cultures prepared from the diencephalon prior to sexual differentiation. More recently, Geert DeVries and his colleagues at the University of Massachusetts created unusual male (XX with *Sry*; see Box A) and female (XY without *Sry*) transgenic mice. In these animals, testes development occurred independently of the X or Y chromosome, thus demonstrating that XY mice with ovaries are, at least in some respects, more masculinized (measured by the density of vasopressin-immunoreactive fibers in the lateral septum) than XX mice with testes. Complex as this configuration of chromosomal sex and phenotype may be, the experiment shows that at least one sexually dimorphic trait (the density of vasopressin fibers in the midbrain) depends on the presence of the Y chromosome, but not on the presence of testes and the androgens they secrete postnatally. This observation supports the notion that hormone-independent sex differences are a part of the developmental plan. This idea has also been examined in birds. Arthur Arnold and his group at the University of California at Los Angeles have shown that the well-known song patterns existing in male but not in female zebra finches are driven in part by genetic mechanisms that operate independently of hormone levels.

These several studies raise the possibility that mechanisms in addition to hormones contribute to the sexual diversity of humans—a point that is important to bear in mind during the following discussion of the hormone-driven sex differences in rodents.

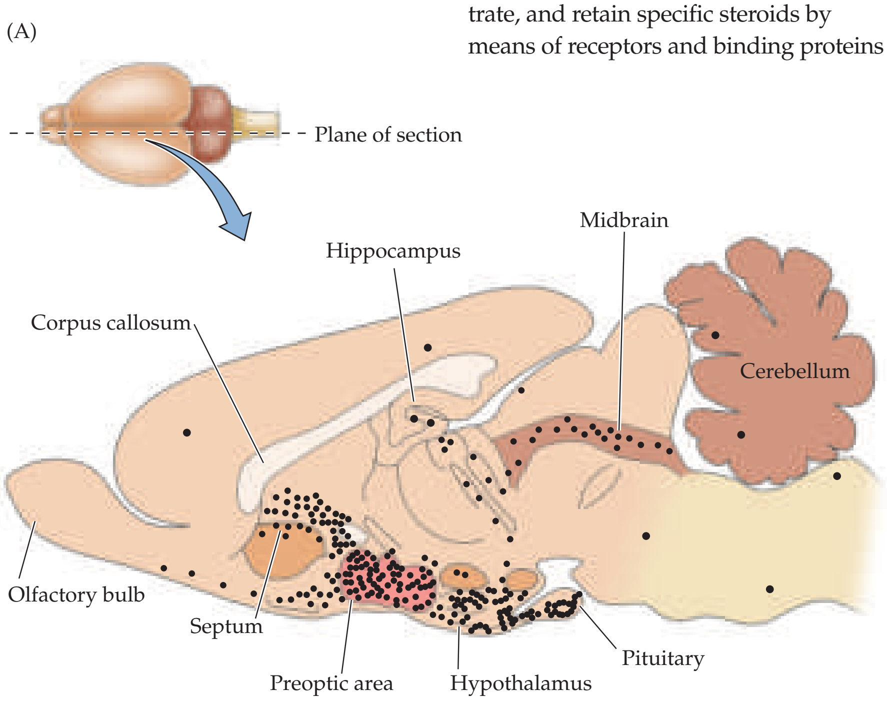
Box C

The Actions of Sex Hormones

Sex hormones, which include progestins, androgens, and estrogens, are all steroids derived from a common precursor, cholesterol (see Figure 29.1). Despite the common tendency to the contrary, it is not really correct to think of estrogens as "female" and androgens as "male." Females and males synthesize both estrogens and androgens, but in ratios that are very different. Both sexes also have androgen and estrogen receptors in the brain, although there are some regional sex differences in receptor density

Because sex steroids are lipids, they do not need membrane receptors to enter cells; they simply diffuse through the lipid bilayer. However, neurons and other cells have the capacity to select, concentrate, and retain specific steroids by means of receptors and binding proteins in both the cytoplasm and nucleus. Different areas of the adult brain have different steroid receptor patterns, with overlapping distributions of receptor types. Thus, particular brain regions can be targets for the actions of different classes of steroids (Figure A). For instance, estradiol receptors are sparsely distributed in the neocortex of rodents, but are prevalent in preoptic and hypothalamic areas and the anterior pituitary. Conversely, whereas receptors for 5-α-dihydrotestosterone (5-DHT) are found only in certain nuclei in the septum and hypothalamus, both estradiol and 5-DHT receptors are abundant in the frontal, prefrontal, and cingulate areas of the cortex.

Some neurons express receptors for more than one steroid and, as a result, hormones can have a synergistic effect. For example, all neurons with progesterone receptors also express estrogen



(A) Distribution of estradiol-sensitive neurons illustrated in a sagittal section of the rat brain. Animals were given radioactively labeled estradiol; dots represent regions where the label accumulated. In the rat, most estradiol-sensitive neurons are located in the preoptic area, hypothalamus, and amygdala. (After McEwen, 1976.)

The Effect of Sex Hormones on Neural Circuitry

Gonadal steroids—whether estrogens or androgens—stimulate sexually dimorphic patterns of development by binding to estrogen or androgen receptors. These receptors, which are transcription factors activated by hormone binding, influence gene transcription and, ultimately, the development of an array of targets, including sexually dimorphic neural circuits. (See Box C for further details about the actions of sex hormones.)

During development, and to some extent throughout life, estradiol stimulates brain dimorphisms by increasing size, nuclear volume, dendritic length, dendritic branching, dendritic spine density, and synaptic connectivity of the sensitive neurons. One of the first demonstrations of such effects was provided by Dominique Toran-Allerand at Columbia University, who receptors. Although female reproductive behaviors can be elicited by estrogen alone, the behavior is greatly facilitated in females given estrogen followed by progesterone.

Steroids can have a direct effect on neural activity by altering the permeability of the membrane to neurotransmitters and their precursors, or by altering the function of neurotransmitter receptors (Figure B). This type of effect has a latency-to-onset of seconds to minutes and makes it possible for sex steroids to explicitly modulate the efficacy of neural signaling.

Sex steroids can also have an indirect effect on neural activity by forming non-covalent bonds with steroid receptors, or by affecting other signaling pathways. Binding to a steroid receptor causes a conformational change that allows the receptor to bind to specific DNA-recognition elements called **hormone-responsive elements**. Steroid receptor co-activators, which are members of a family of co-activators that modulate the activity of steroid receptors, can enhance the effects of steroids by (1) opening up chromatin structure and (2) stabilizing the preinitiation complex at the level of the relevant promoter. Consequently, hormones can alter gene expression, leading to changes in the synthesis of specific proteins (Figure B). Such indirect hormonal actions have a latency-to-onset of minutes to hours.

Most sexually dimorphic differences in the brains of females and males are thought to arise by the indirect actions of hormones on gene expression.

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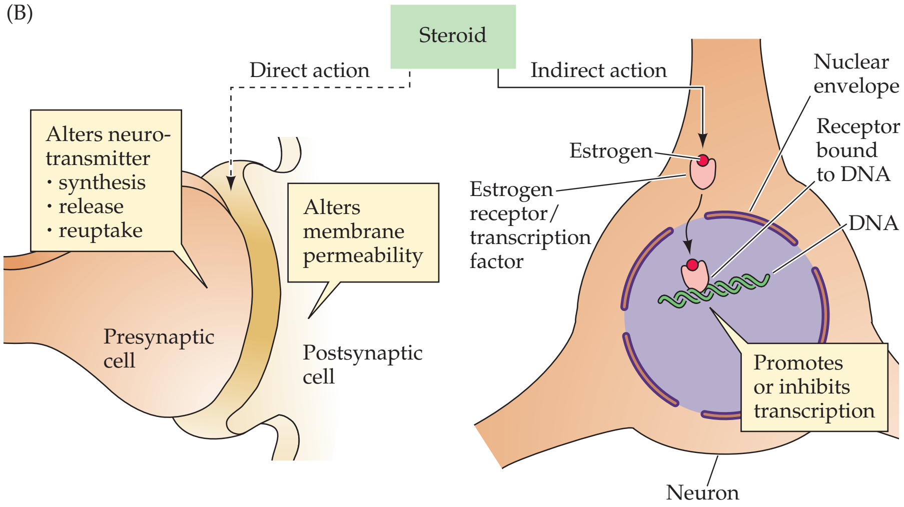


(B) Steroids have direct and indirect effects on neurons. Dashed line shows direct effects of hormones on the pre- or postsynaptic membrane, which alters neurotransmitter release, and affects neurotransmitter receptors. Solid line shows indirect effects of hormones, which act at the level of the nucleus to alter protein synthesis. (After McEwen et al., 1978.)

noted the striking consequences of adding estrogens to fetal hypothalamic explants (Figure 29.2). Estradiol can also stimulate an increase of the number of synaptic contacts neurons receive in adult animals. For example, during periods of high circulating estrogen in the estrous cycle of female rodents (or after administration of estrogens) there is an increase in the density of spines and synapses on the apical dendrites of pyramidal neurons in the hippocampus (Figure 29.3). These changes in neuronal circuitry presumably underlie differences in learning and memory over the estrous cycle (e.g., differences in the spatial navigation of rodents).

Other hormonally generated differences in brain circuits leading to differences in reproductive behaviors in both female and male rodents have been documented by administering testosterone (or estrogens) to females, or by

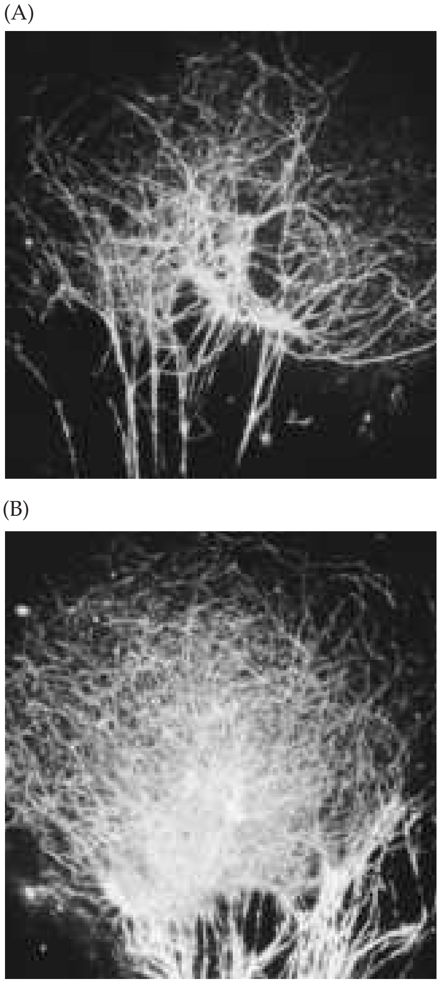


Figure 29.2 Estrogen causes exuberant outgrowth of neurites in hypothalamic explants from newborn mice. (A) Control explant showing only a few silver-impregnated processes growing from the explant. (B) An estradiol-treated explant has many more neurites growing from its center. (From Toran-Allerand, 1978.)

depriving males of testosterone by castrating them at birth. Geoffrey Raisman and Pauline Field, then working at Oxford University, found a greater number of synapses on spines in the preoptic region of the hypothalamus in normal female rats compared to the equivalent region in males. This difference is directly under the influence of hormones during development. Castrating males within 12 days of birth increased the density of these synapses to female levels, whereas administration of testosterone to developing females led to a reduction of preoptic spine synapses to male levels. Neonatal castration also affects other aspects of brain function. Unlike intact males, male rats castrated soon after birth respond to estradiol with a surge of luteinizing hormone (which, in the presence of ovaries, would lead to ovulation); and treatment of newborn females with testosterone leads to the loss of the luteinizing hormone surge.

Subsequently, Roger Gorski and his colleagues at the University of California at Los Angeles discovered a nucleus in the male rodent hypothalamus that is so small as to be essentially missing in the female; logically enough, they called this structure the sexually dimorphic nucleus (SDN). This sex difference also develops under the influence of hormones; Gorski found that the SDN in male rats could be reduced in size to that of the female by castration within the first 2 weeks after birth. Similarly, the size of the female SDN could be increased to that of the male by early administration of androgens. Since the preoptic area is crucial for the display of male sex behavior in many species, the sex difference in the SDN seemed likely to be related to male sexual function. Indeed, female rodents given testosterone early in development exhibit mounting behavior, whereas male rodents deprived of testosterone exhibit lordosis (i.e., a behavior receptive to mounting). Nonetheless, the exact role of the SDN plays in these behavioral sex differences is not clear.

In short, the development of sexually dimorphic structures in the rodent brain is primarily under the control of circulating sex hormones, with some determined at least in part by genes on the Y chromosome. Again, the effect of hormones is less certain and may be more complex in the primate brain. For example, Kim Wallen at Emory University investigated the role of social conditions in establishing some of the sex-typical behaviors of rhesus monkeys that were once thought to be solely determined by hormones. He found that although rough-and-tumble play and mounting (typical juvenile behavior for this species) were exhibited less frequently by females than by males, the environment in which the animals were reared affected the degree of this sex difference. Moreover, when reared with only their own sex, males displayed more and females less of these behaviors. Thus, while the propensity for such sex-typical juvenile behaviors may be established by hormonal actions, their expression is shaped by the environment in which the animal develops. It is not difficult to extrapolate from these studies to humans, where it seems especially important to consider both nature and nurture in the development of differences between sexes.

Other Central Nervous System Dimorphisms Specifically Related to Reproductive Behaviors

Other sexual dimorphisms in the central nervous system influence behaviors ranging from the control of motor responses in reproductive behaviors to aspects of cognition. This section briefly reviews additional examples specifically related to reproductive behavior; the following section considers sexual dimorphisms related to cognitive abilities.

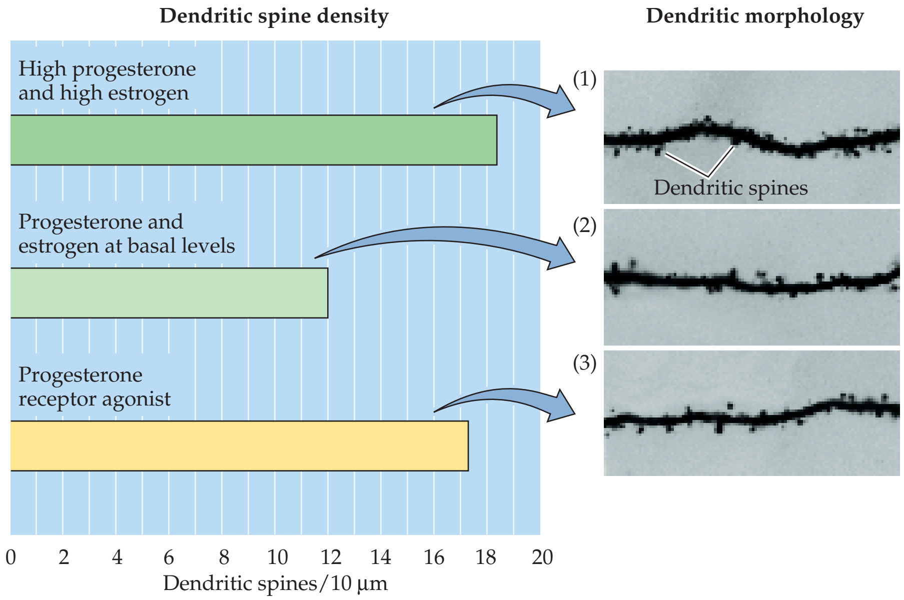
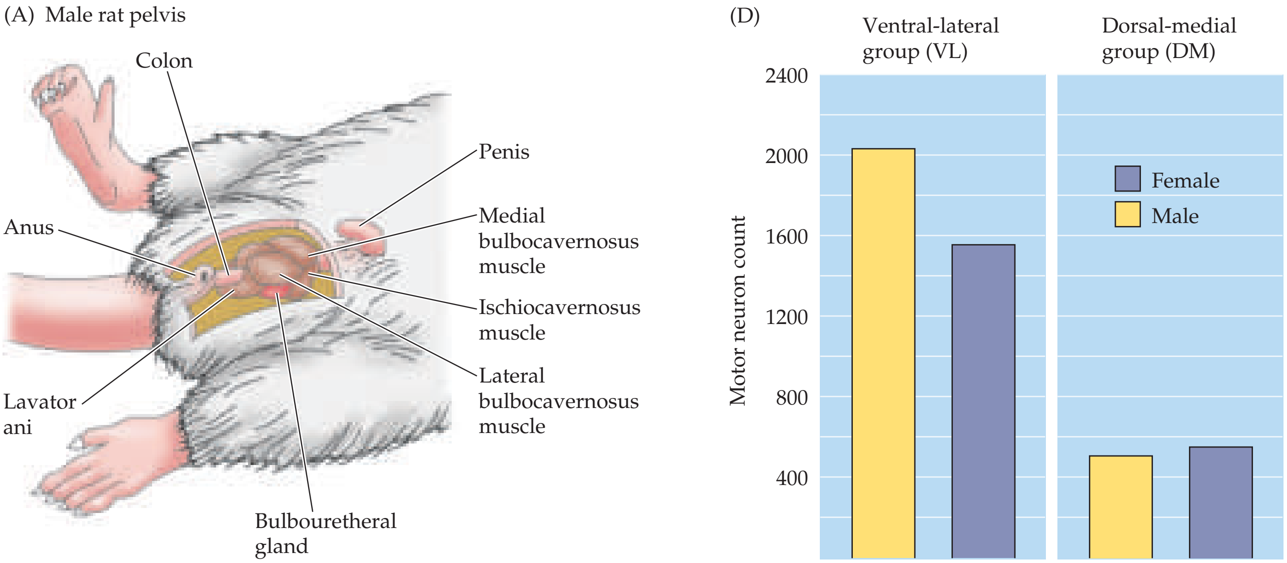
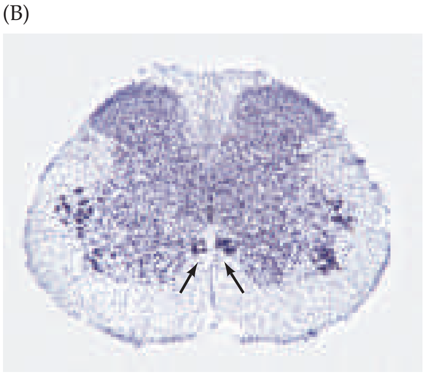


Figure 29.3 Changes in the dendrites of rat hippocampal neurons following various hormonal regimes. *Left:* Dendritic spine density under each of the indicated conditions (recall that dendritic spines, which are small extensions from the dendritic shaft, are sites of synapses). *Right:* Tracings of representative apical dendrites from hippocampal pyramidal neurons: (1) After administration of progesterone and estrogen in high dosage. (2) After administration of progesterone and estrogen at basal levels. (3) After administration of a progesterone receptor antagonist. (After Woolley and McEwen, 1992.)

Perhaps the best example of sexual dimorphism related to motor control of a reproductive behavior is the difference in size of a nucleus in the lumbar segment of the rat spinal cord called the **spinal nucleus of the bulbocavernosus**. The motor neurons of this nucleus innervate two striated muscles of the perineum, the bulbocavernosus and levator ani (Figure 29.4A). In males, the bulbocavernosus and levator ani attach to the penis and play a role both in urination and copulation. In female rats, the bulbocavernosus is absent and the levator ani is dramatically reduced in size. Marc Breedlove and his colleagues first showed that the spinal nucleus containing the motor neurons that innervate the bulbocavernosus is absent in female rats but is quite large in males (Figure 29.4B,C). Breedlove and Nancy Forger then demonstrated that the development of this dimorphism in the spinal cord depends on the maintenance of target muscles by circulating androgens. Since developing males have high levels of circulating sex steroids and females do not, these muscles largely degenerate in developing female rats, leaving the motor neurons to atrophy in the absence of trophic support (see Chapter 23).

As with most sexual dimorphisms, the analogous situation in humans is considerably less clear than in experimental animals. In humans, the spinal cord structure that corresponds to the spinal nucleus of the bulbocavernosus in rats is called **Onuf's nucleus**. Onuf's nucleus consists of two cell groups in the sacral cord, the dorsal medial and the ventral lateral groups. The dorsal medial group is not sexually dimorphic; however, human females have fewer neurons in the ventral lateral group than males (Figure 29.4D). In con-





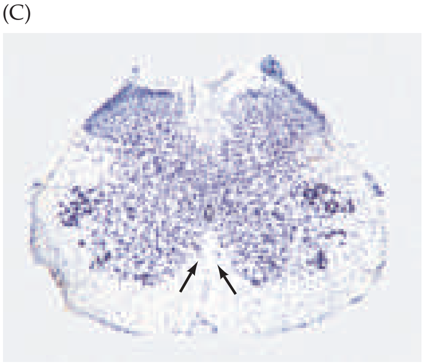


Figure 29.4 The number of spinal motor neurons related to the perineal muscles is different in female and male rodents. (A) Diagram of the perineal region of a male rat. (B) A histological cross section through the fifth lumbar segment of the male. Arrows indicate the spinal nucleus of the bulbocavernosus. (C) Same region of the spinal cord in the female rat. There is no equivalent grouping of densely stained neurons. (D) Histograms showing motor neuron counts in the dorsal-medial and ventral-lateral groups of Onuf's nucleus in human females and males. (A after Breedlove and Arnold, 1984; B and C from Breedlove and Arnold, 1983; D after Forger and Breedlove, 1986.)

trast to rodents, human females retain a bulbocavernosus muscle throughout life (which serves to constrict the vagina), but the muscle is smaller than in the male. The difference in nuclear size in humans, as in rats, presumably reflects the difference in the number of muscle fibers the motor neurons must innervate.

A variety of reproductive behaviors, including desire, priming, and parenting behaviors, are governed by the hypothalamus. Neurons in the medial preoptic area of the primate anterior hypothalamus apparently mediate at least some of these behaviors (Figure 29.5). In rhesus monkeys, physiological recordings from hypothalamic neurons during sexual activity show that neurons of the medial preoptic area of the anterior hypothalamus fire during different components of the sexual act. Such recordings have been carried out on male monkeys sitting in a flexible restraining chair that allows the male to gain access to a receptive female by pressing a bar, which brings the female close enough to allow the male to mount her. In this way, the responses of hypothalamic neurons can be correlated with "desire" (number of bar presses) and mating behavior (contact, mounting, intromission, thrusting). Neurons in the medial preoptic area of the male hypothalamus fire rapidly before sexual behavior, but decrease their activity upon contact with the female and mating (Figure 29.6). In contrast, neurons in the dorsal anterior hypothalamus begin firing at the onset of mating and continue to fire vigorously during intercourse. Although these studies do not speak to sexual dimorphism, they provide direct evidence about the variety of sexual behaviors mediated by the hypothalamus.

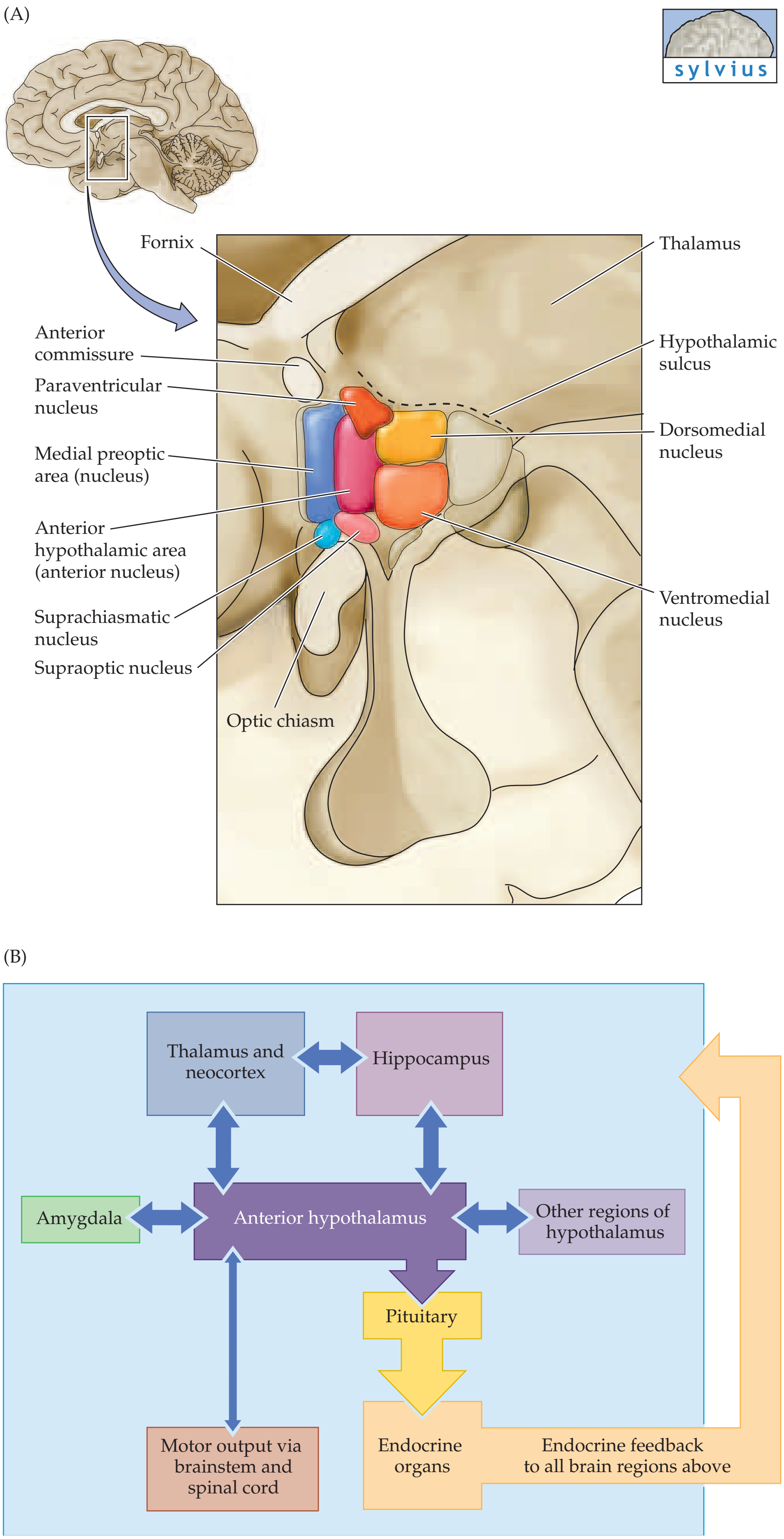

(A)
sylvius
Fornix
Thalamus
Anterior commissure
Paraventricular nucleus
Hypothalamic sulcus
Dorsomedial nucleus
Medial preoptic area (nucleus)
Anterior hypothalamic area (anterior nucleus)
Suprachiasmatic nucleus
Ventromedial nucleus
Supraoptic nucleus
Optic chiasm
(B)
Thalamus and neocortex
Hippocampus
Amygdala
Anterior hypothalamus
Other regions of hypothalamus
Pituitary
Motor output via brainstem and spinal cord
Endocrine organs
Endocrine feedback to all brain regions above

Figure 29.5 Organization of the components of the hypothalamus involved in regulating sexual functions. (A) The human hypothalamus, illustrating the location of the anterior hypothalamic area and other nuclei in which sexual dimorphisms have been observed in either humans or experimental animals. (B) Diagram of the major relationships of the anterior hypothalamus with other brain regions. Blue arrows denote neural connections; yellow arrows denote hormonal links; purple arrow denotes a combination of hormonal and neural connections. Although this information comes largely from studies of rodents, it is reasonable to assume that these interactions are characteristic of mammals.

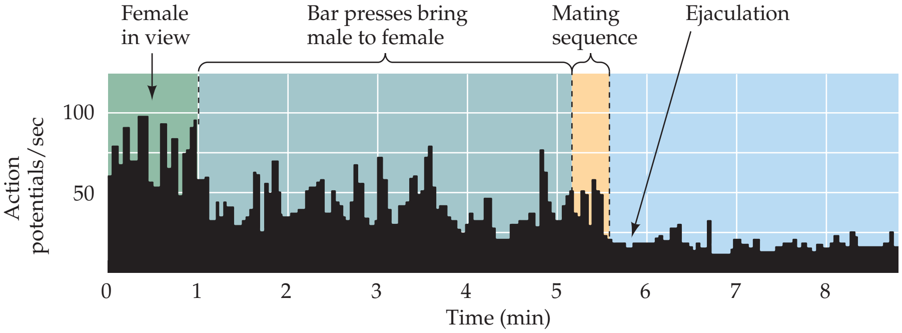


Figure 29.6 Many neurons in the primate hypothalamus are actively associated with sexual behavior. This example shows a histogram of neuronal activity recorded in the medial preoptic area in a male monkey exposed to a receptive female (see text). The firing rate of the neuron changes during different phases of sexual activity. (After Oomura et al., 1983.)

Such studies of rodents and non-human primates have stimulated a variety of further observations in the human hypothalamus. The most thoroughly documented examples of sexually dimorphic hypothalamic nuclei in humans have been described by Laura Allen and Roger Gorski at the University of California at Los Angeles and by Dick Swaab and his colleagues at the Netherlands Institute for Brain Research. Swaab first found a sex difference in the anterior hypothalamus of humans in a cell group that they named the sexually dimorphic nucleus (by analogy with the SDN of rats). Subsequently, Allen and Gorski discovered that there are actually four cell groupings within the anterior hypothalamus of humans, which they called the **interstitial nuclei of the anterior hypothalamu**s (**INAH**). The INAH are numbered 1 to 4, from dorsolateral to ventromedial; INAH-1 corresponds to the nucleus initially discovered by Swaab (Figure 29.7). Allen and Gorski reported that INAH-2 and INAH-3 can be more than twice as large in males as they are in females.

What might account for these somewhat discrepant findings? First, human studies are always complicated by the difficulty of obtaining human brains that meet the criteria of uniformity applied to the brains of experimental animals. Second, it takes a long time to acquire a large enough number of human brains to confidently interpret the results. Swaab and colleagues suggested that INAH-1 and 2 change in size over time; thus the age of the subjects studied might also influence observed sex differences. For instance, INAH-1 is evidently about the same size in females and males up until 2–4 years of age; it then becomes larger in males until approximately 50 years of age, when it decreases in size in both sexes. Although generally larger in males, INAH-2 is larger in females of childbearing age than in prepubescent and postmenopausal females. Changes in nuclear size with age in humans presumably arise as a result of changing levels of circulating sex steroids.

Despite the difficulties inherent in the interpretation of such studies, one aspect of human reproduction in which these hypothalamic nuclei have been implicated is the choice of a sexual partner. In addition to heterosexual behavior, some humans express sexual behaviors toward both females and males (**bisexuality**), and some only toward members of their own phenotypic sex (**homosexuality**). Still other people are interested the opposite sex

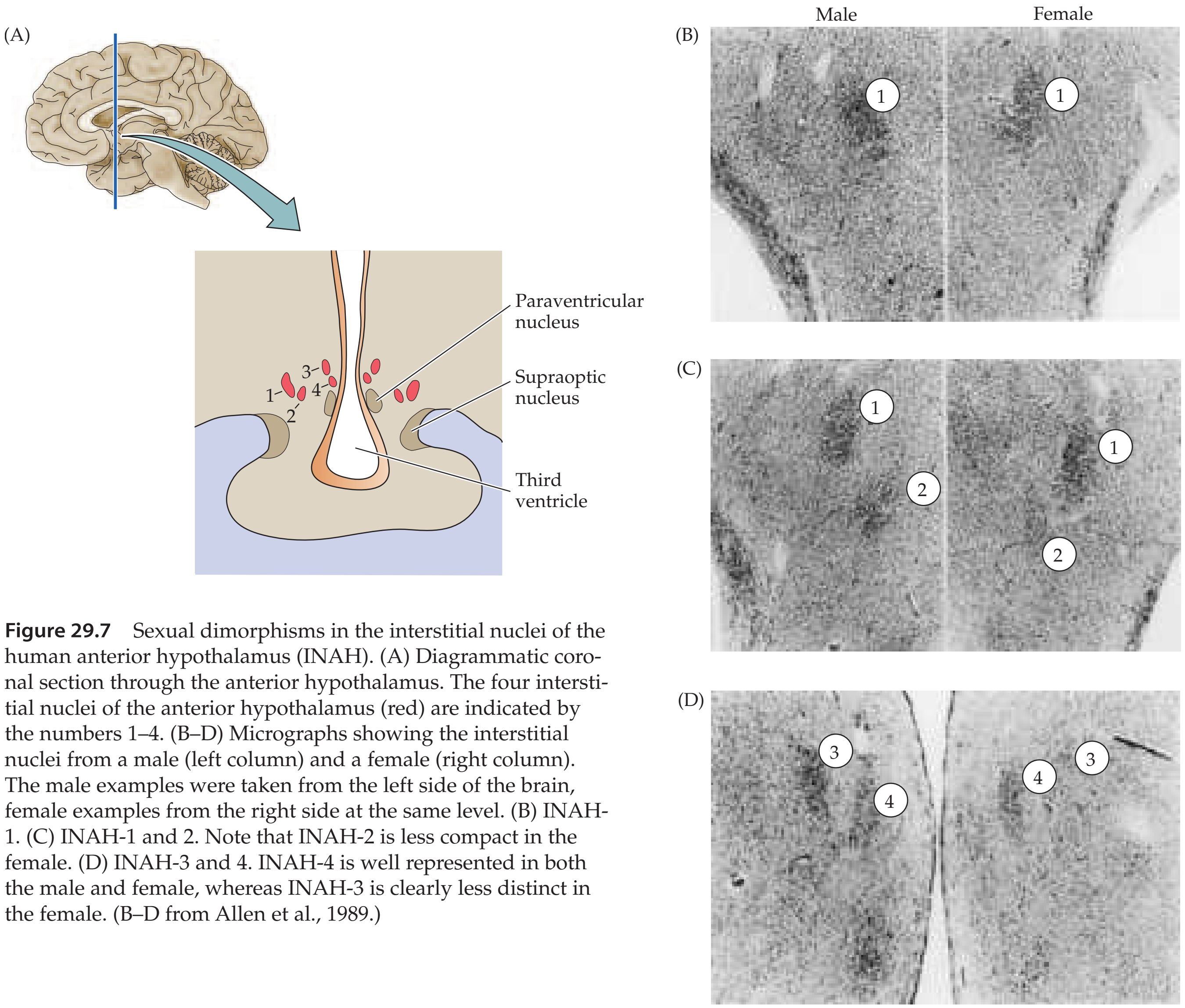
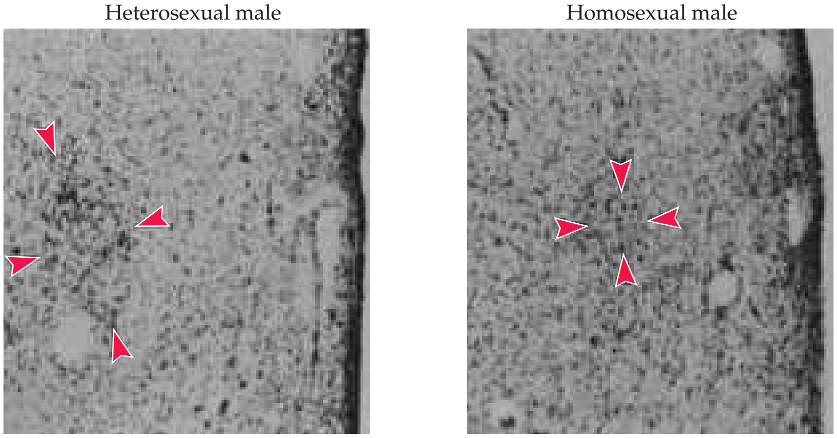


Figure 29.7 Sexual dimorphisms in the interstitial nuclei of the human anterior hypothalamus (INAH). (A) Diagrammatic coronal section through the anterior hypothalamus. The four interstitial nuclei of the anterior hypothalamus (red) are indicated by the numbers 1–4. (B–D) Micrographs showing the interstitial nuclei from a male (left column) and a female (right column). The male examples were taken from the left side of the brain, female examples from the right side at the same level. (B) INAH-1. (C) INAH-1 and 2. Note that INAH-2 is less compact in the female. (D) INAH-3 and 4. INAH-4 is well represented in both the male and female, whereas INAH-3 is clearly less distinct in the female. (B–D from Allen et al., 1989.)

but with a gender identity that is at odds with their phenotypic sex (**transgenderism**). Based on experimental work in animals and evidence that relatively simple sexual behaviors are influenced by brain dimorphisms, explaining these more complex behaviors in the same general way has been an attractive possibility. To investigate this issue, Simon LeVay, then working at the Salk Institute, compared the INAH of females, heterosexual males, and homosexual males. LeVay first confirmed Allen and Gorski's findings that of the four INAH nuclei, at least two are sexually dimorphic. He went on to discover that one of these nuclei—INAH-3—is more than twice as large in male heterosexuals as in male homosexuals (Figure 29.8A) and suggested that this difference is related to sexual orientation.

These studies have since been replicated by William Byne at the Mount Sinai School of Medicine, who confirmed the sexual dimorphism in INAH-3, although the difference was less than that reported by Allen and by LeVay. Byne concluded that INAH-3 in the gay men studied was intermediate in

(A) INAH-3



(B) Suprachiasmatic nucleus

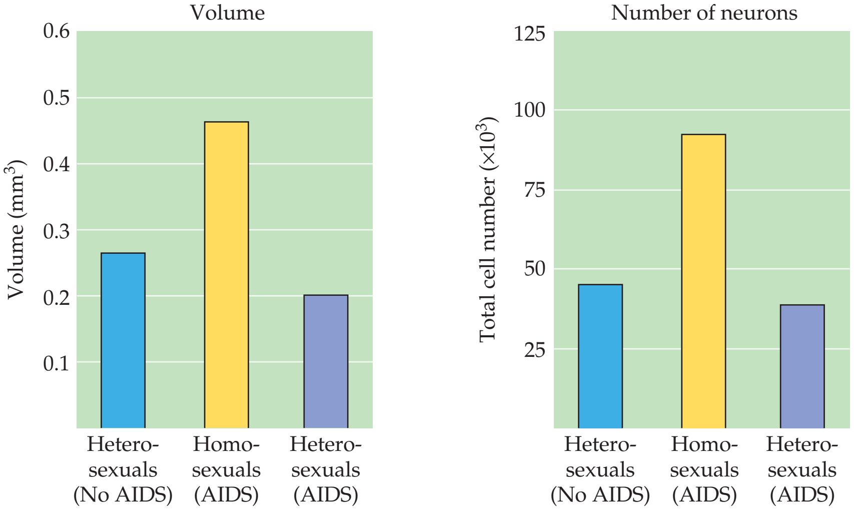


Figure 29.8 Brain dimorphisms in heterosexual and homosexual human males. (A) Micrographs showing difference in INAH-3 between heterosexual and homosexual males. Arrowheads outline the nucleus. (B) The suprachiasmatic nucleus may also differ between homosexual and heterosexual males. The suprachiasmatic nucleus of homosexual males appears to be larger (left histogram) and to contain more neurons (right histogram) than that of heterosexual males with or without AIDS (which could be a significant variable in such studies). (A from LeVay, 1991; B after Swaab and Hofman, 1990.)

size between heterosexual men and women. The difference between the size of INAH-3 in the heterosexual and gay men in the study was of borderline significance, and thus neither a strong confirmation nor a refutation of earlier work.

Other researchers have suggested that dimorphisms of additional hypothalamic nuclei are related to sexual orientation and gender identity. Dick Swaab and Michel Hofman at the Netherlands Institute for Brain Research studied the *suprachiasmatic nucleus* of the hypothalamus, which lies just above the optic chiasm in both rodents and humans and generates circadian rhythms (see Figure 29.5A and Chapter 27). In examining the suprachiasmatic nuclei of females, heterosexual males, and homosexual males, Swaab and Hofman found the volume of the suprachiasmatic nucleus to be almost twice as large in male homosexuals compared to male heterosexuals (Figure 29.8B). They found no difference, however, between the size of the suprachiasmatic nucleus in females and heterosexual males. Like LeVay, they suggested that the difference in nuclear size between homosexual and heterosexual men might be related to sexual orientation. This same group reported another dimorphism that may be related to gender identity. In comparing male-to-female transgendered individuals to non-transgendered males, they found that another hypothalamic structure, the *bed nucleus of the stria terminalis*, is smaller in transgendered males, being closer in size to that of females.

The history of these several research efforts highlights the difficulty of carrying out controlled studies that measure small differences in the human brain and the importance of reliable replication. Taken together, however, the sum of this evidence suggests a plausible explanation of the continuum of human sexuality: small differences in the relevant brain structures generate significant differences in sexual identity and behavior. By analogy with rodents, it seems likely these human brain dimorphisms are established by the early influence of hormones acting on the brain nuclei that mediate various aspects of sexuality. For instance, low levels of circulating androgens in a male early in life could lead to a relatively feminine brain in chromosomal males, whereas high levels of circulating androgens in females could lead to a relatively masculinized brain in chromosomal females.

As attractive as this hypothesis may be, the development of sexuality in humans is almost certainly a good deal more complicated. Although LeVay's findings support the idea that homosexuality is related to "feminization" of the male brain (recall that INAH-3 in gay males is smaller than in straight males), Swaab and Hofman's data on the size of the suprachiasmatic nucleus undermine the interpretation that the male homosexual's brain is simply "feminized" by a lack of androgens early in development. Whereas they found a difference in the volume of this suprachiasmatic nucleus between homosexual and heterosexual males, in contrast to LeVay they found no difference in the volume of this nucleus between females and heterosexual males. In addition, the development of the INAH-1 dimorphism (see above) occurs between 2 and 4 years of age—long after the first testosterone surge in males. These discrepancies suggest that the development of sexually dimorphic nuclei in humans does not depend solely on early hormone levels.

As discussed earlier, genetic effects of the Y chromosome independent of those influencing the production of hormones can affect sexually dimorphic traits. It should also be remembered that adult neural circuits also have some plasticity (see Chapter 24 and the following section), leaving open the possibility that behavior, experience, and changes in circulating hormone levels combine to generate dimorphisms at later life stages. In apparent confirmation of this suggestion, Breedlove and colleagues have reported that the posterodorsal nucleus of the medial amygdala has a greater volume in male rats than in female, but that castration of adult males and androgen treatment of adult females reverses this effect. Thus, the question of whether we are simply "born that way" with respect to sexuality remains difficult to answer. Like most developmental events, a combination of intrinsic and extrinsic factors are involved.

Despite all these uncertainties, work over the last decade has clearly placed human sexuality on a much firmer biological footing. This is a welcome advance over the not-too-distant past when unusual sexual behavior was commonly explained in social, Freudian, or moralistic terms.

Brain Dimorphisms Related to Cognitive Function

Evidence for sexually dimorphic behavior in humans that is not directly related to reproductive functions comes mainly from clinical observations. For example, neurologists have reported that females suffer aphasia less often than males after damage to the left hemisphere. This observation led to the suggestion that language functions are to some degree differently represented in females and males. To explore this issue, Doreen Kimura at the University of Western Ontario looked at the language ability in right-handed patients with unilateral lesions of the left cerebral cortex. She found that females were more likely to suffer aphasia if the damage was to the anterior left hemisphere, whereas males were more likely to suffer aphasia if the damage was located posteriorly. Kimura's data suggest that language areas of the female brain are more anteriorly represented and thus less vulnerable to stroke.

Susan Rossell and her colleagues at University College London have suggested other such sexual dimorphisms in the human brain. Using fMRI to measure activation during a lexical visual field task (a language task that shows replicable sex differences related to speed and accuracy), Rossell and colleagues found more brain activity in response to such challenges in females than in males. Females show greater activation of the right hemisphere areas, especially in the inferior frontal, inferior posterior, and middle temporal gyri. In addition, females have a left visual field advantage when the task is presented visually, showing faster reaction times than males. In males, activation is more lateralized to the left hemisphere, especially the inferior posterior temporal lobe and the fusiform and lingual gyri. These studies and the earlier work by Kimura suggest that females and males use overlapping but somewhat different cortical areas to carry out language tasks.

The performance of tasks that depend more on one hemisphere than the other has also been examined in females and males. One simple test for visuospatial differences entails how well girls and boys are able to identify shapes after feeling them with the right or left hand while blindfolded. Both sexes perform equally well with either hand up to about 6 years of age. Thereafter, boys start scoring better when they use their left hand, whereas girls continue to score equally well with either hand up to 13 years of age, when they also begin to do better with their left hand. This study suggests that boys develop the right hemispheric lateralization of visuospatial skills earlier than girls.

The idea that females and males develop lateralized functions at different rates is supported by studies of the development of the prefrontal cortex of non-human primates. Removing the prefrontal cortex before 15 to 18 months of age does not affect motor-planning functions in female rhesus monkeys, although the same lesion in male monkeys at this age diminishes these skills.

In a similar vein, Matthias Riepe and his colleagues at the University of Ulm have reported that human females and males use different strategies to navigate in an unfamiliar environment. Males trying to find their way out of a three-dimensional virtual reality maze use the geometry of the whole scene and "escape" from the maze in a little more than 2 minutes on average. Females tend to use local landmarks or clues and take about a minute longer to get out. Functional brain imaging shows that both sexes use the right hippocampus during this task, but that men use the left hippocampus as well. Conversely, women tend to use the right prefrontal cortex, whereas men do not. Involvement of the inferior parietal lobe is also different in females and males. The two sides of this structure are thought to mediate different aspects of visual processing, with the left side more involved in perceptions such as judging how fast something is moving or mentally rotating three-dimensional objects, and the right side mediating working memory of spatial relationships. Finally, Godfrey Pearlson and his colleagues at Johns Hopkins University have determined that the right parietal lobe is larger than the left in females, whereas in males the left parietal lobe is larger than the right.

None of these studies is in itself compelling, but taken together they support the idea that the two sexes to some degree use different cognitive strategies, and that these differences affect some aspects of behavior.

Hormone-Sensitive Brain Circuits in Adult Animals

As mentioned earlier, there is growing evidence that some brain circuits continue to change over the course of an individual's life, depending on both experience and hormonal milieu. For example, changes in the brain circuits of adult rats occur in conjunction with parenting behavior. Michael Merzenich, Judith Stern and their colleagues at the University of California at San Francisco have shown that the cortical representation of the ventrum (chest wall) is altered in the somatic sensory cortex of the lactating female. As determined by electrophysiological mapping, the representation of the ventrum is approximately twice as large in nursing females as in non-lactating controls. Moreover, the receptive fields of the neurons representing the skin of the ventrum in lactating females are decreased to about a third of that of non-lactating females (Figure 29.9). Both the increase in cortical representation and the decrease in receptive field size highlight the fact that changes in behavior can be reflected in changes of cortical circuitry in adult animals.

Another example of adult plasticity under hormonal control is the altered connections between cells of the female rat hypothalamus after giving birth. In females prior to pregnancy, the relevant hypothalamic neurons are isolated from each other by thin astrocytic processes. Under the influence of the hormonal environment prevailing during birth and lactation, the glial processes retract and the oxytocin- and vasopressin-secreting neurons become electrically coupled by gap junctions (Figure 29.10). Before the female gives birth, these neurons fire independently; during lactation, however, they fire synchronously, releasing pulses of oxytocin into the maternal circulation. These surges of oxytocin cause the contraction of smooth muscles in the mammary glands, and hence milk ejection. Interestingly, the changes are thought to be mediated by olfactory cues, since the lactating circuits can be induced in virgin females simply by placing them in the vicinity of pups.

These examples of adult plasticity suggest that some of the sexual circuits of the brain are malleable not only during development, but to some degree throughout life under the effects of experience and the changing hormonal milieu.

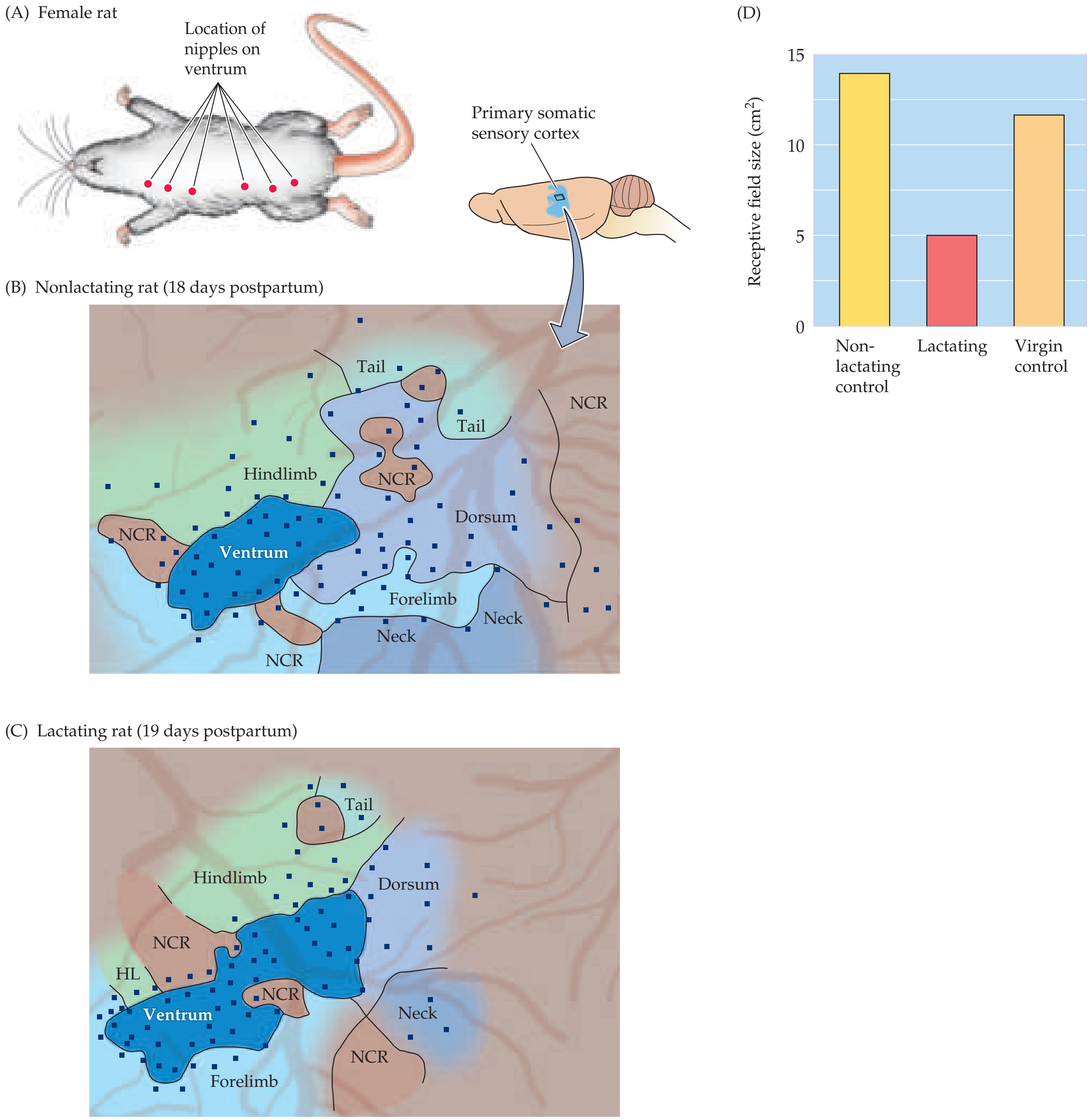

(A) Female rat
Location of nipples on ventrum
Primary somatic sensory cortex
(B) Nonlactating rat (18 days postpartum)
Tail
Tail
NCR
Hindlimb
NCR
Dorsum
NCR
Ventrum
Forelimb
Neck
Neck
NCR
(C) Lactating rat (19 days postpartum)
Tail
Hindlimb
Dorsum
NCR
HL
NCR
Ventrum
Neck
NCR
Forelimb
(D)
Receptive field size (cm²)
15
10
5
0
Non-lactating control
Lactating
Virgin control

Figure 29.9 Changes in the cortical representation of the chest wall in the rat primary somatic sensory cortex during lactation. (A) Ventrum of the female rat; dots mark the position of nipples. (B) Diagram of somatic sensory cortex in a nonlactating control rat, showing the amount of cortex normally activated by stimulation of the ventrum. Squares mark electrode penetrations; colors signify the estimated representation. (C) Similar diagram from a 19-day postpartum, lactating rat. Note the expansion of the representation of the ventrum. NCR, no cutaneous response. (D) Histogram of receptive field sizes of single neurons in nonlactating control, lactating, and virgin control rats. The receptive field sizes of neurons in lactating mothers are decreased. (B–C after Xerri et al., 1994.)

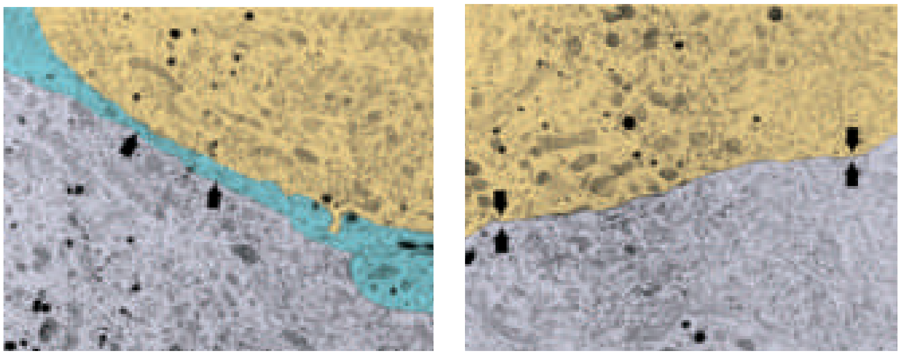


Figure 29.10 Changes in neurons of the rat supraoptic nucleus during lactation. *Left:* Before birth, the relevant neurons and their dendrites are isolated from each other by astrocytic processes (blue). *Right:* During nursing of the young, the astrocytic processes withdraw, and neurons and their dendrites show close apposition (arrow pairs) that allows electrical synapses to form between adjacent neurons (see Chapter 5). (From Modney and Hatton, 1990.)

Summary

Differences in female and male behaviors ranging from copulation to cognition are linked to differences in brain structure. Although the neural basis for these sexual dimorphisms is much clearer in experimental animals, the evidence for sex-related differences in the human brain has grown rapidly in recent years. The region of the brain in which the most clear-cut structural dimorphisms occur is the anterior hypothalamus, which governs reproductive behavior. In rats and monkeys, the nuclei in this region play a role not only in the mechanics of sex, but also in desire, parenting, and sexual orientation. In the rodent, sexual dimorphisms develop primarily as a result of hormonal action on neurons during early development. On the strength of this knowledge about sexual development in experimental animals, neurobiological explanations for a variety of human sexual behaviors have been proposed. Such models remain controversial because the sexual dimorphisms of the human brain and their functional significance are neither fully established nor well understood. In addition, only a few such studies have been replicated. Nevertheless, it seems likely that a deeper understanding of how the dynamic interplay between behavior, genetics, hormones, and environment influence the brain throughout life will eventually explain the fascinating continuum of human sexuality.

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Chapter 30

Memory

Overview

One of the most intriguing of the brain's complex functions is the ability to store information provided by experience and to retrieve much of it at will. Without this ability, many of the cognitive functions discussed in the preceding chapters could not occur. *Learning* is the name given to the process by which new information is acquired by the nervous system and is observable through changes in behavior. *Memory* refers to the encoding, storage, and retrieval of learned information. Equally fascinating (and important) is the normal ability to forget information. Pathological forgetfulness, or amnesia, has been especially instructive about the neurological underpinnings of memory; amnesia is defined as the inability to learn new information or to retrieve information that has already been acquired. The importance of memory in daily life has made understanding these several phenomena one of the major challenges of modern neuroscience, a challenge that has only begun to be met. The mechanisms of plasticity that provide plausible cellular and molecular bases for some aspects of information storage have been considered in Chapters 22 through 24. The present chapter summarizes the broader organization of human memory, surveys the major clinical manifestations of memory disorders, and considers the implications of these disorders for ultimately understanding human memory in more detailed terms.

Qualitative Categories of Human Memory

Humans have at least two qualitatively different systems of information storage, which are generally referred to as **declarative memory** and **nondeclarative memory** (Figure 30.1; see also Box A). Declarative memory is the storage (and retrieval) of material that is available to consciousness and can be expressed by language (hence, "declarative"). Examples of declarative memory are the ability to remember a telephone number, a song, or the images of some past event. Nondeclarative memory (sometimes referred to as *procedural memory*), on the other hand, is not available to consciousness, at least not in any detail. Such memories involve skills and associations that are, by and large, acquired and retrieved at an unconscious level. Remembering how to dial the telephone, how to sing a song, how to efficiently inspect a scene, or making the myriad associations that occur continuously are all examples of memories that fall in this category. It is difficult or impossible to say how we do these things, and we are not conscious of any particular memory during their occurrence. In fact, thinking about such activities may actually inhibit the ability to perform them efficiently (thinking about exactly how to stroke a tennis ball or swing a golf club often makes matters worse).

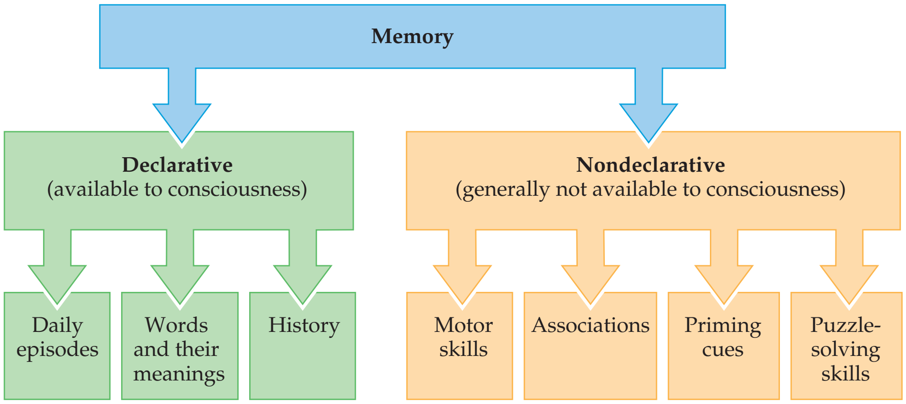

Memory
Declarative
(available to consciousness)
Nondeclarative
(generally not available to consciousness)
Daily episodes
Words and their meanings
History
Motor skills
Associations
Priming cues
Puzzle-solving skills

Figure 30.1 The major qualitative categories of human memory. Declarative memory includes those memories that can be brought to consciousness and expressed as remembered events, images, sounds, and so on. Nondeclarative, or procedural, memory includes motor skills, cognitive skills, simple classical conditioning, priming effects, and other information that is acquired and retrieved unconsciously.

While it makes good sense to divide human learning and memory into categories based upon the accessibility of stored information to conscious awareness, this distinction becomes problematic when considering learning and memory processes in animals. From an evolutionary point of view, it is unlikely that declarative memory arose *de novo* in humans with the development of language. Although some researchers continue to argue for different classifications in humans and other animals, recent studies suggest that similar memory processes operate in all mammals and that these memory functions are subserved by homologous neural circuitry. In other mammals, declarative memory typically refers to the storage of information which could, in principle, be declared through language (e.g., "the cheese is in the box in the corner") and that is dependent on the integrity of the medial temporal lobe and its associated structures (discussed later in the chapter). Nondeclarative memory in other animals, as in humans, can be thought of as referring to the learning and storage of sensory associations and motor skills that are not dependent on the medial temporal portions of the brain.

Temporal Categories of Memory

In addition to the types of memory defined by the nature of what is remembered, memory can also be categorized according to the *time* over which it is effective. Although the details are still debated by both psychologists and neurobiologists, three temporal classes of memory are generally accepted (Figure 30.2). The first of these is **immediate memory**. By definition, immediate memory is the routine ability to hold ongoing experiences in mind for

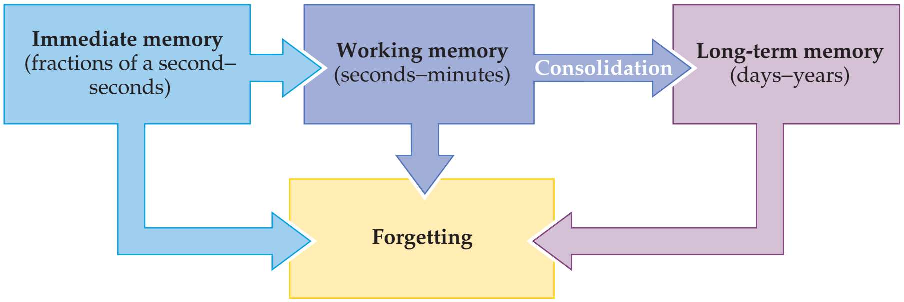
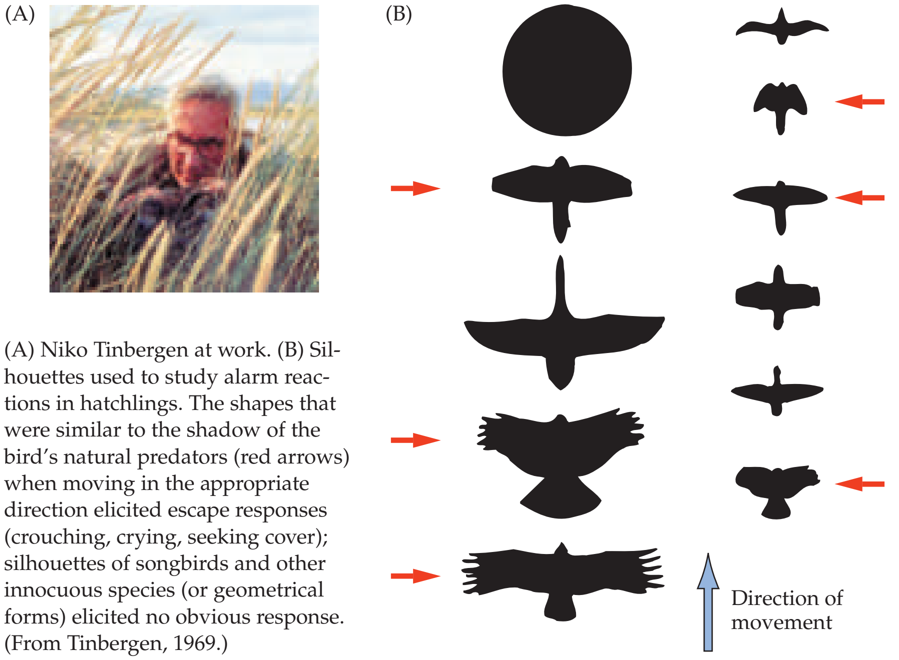

Immediate memory
(fractions of a second–seconds)
Working memory
(seconds–minutes)
Consolidation
Long-term memory
(days–years)
Forgetting

Figure 30.2 The major temporal categories of human memory.

Box A
Phylogenetic Memory

A category of information storage not usually considered in standard accounts is memories that arise from the experience of the species over the eons, established by natural selection acting on the cellular and molecular mechanisms of neural development. Such stored information does not depend on postnatal experience, but on what a given species has typically encountered in its environment. These "memories" are no less consequential than those acquired by individual experience and are likely to have much underlying biology in common with the memories established during an individual's lifetime. (After all, phylogenetic and ontogenetic memories are based on neuronal connectivity.)



(A) Niko Tinbergen at work. (B) Silhouettes used to study alarm reactions in hatchlings. The shapes that were similar to the shadow of the bird's natural predators (red arrows) when moving in the appropriate direction elicited escape responses (crouching, crying, seeking cover); silhouettes of songbirds and other innocuous species (or geometrical forms) elicited no obvious response. (From Tinbergen, 1969.)

Information about the experience of the species, as expressed by endogenous or "instinctive" behavior, can be quite sophisticated, as is apparent in examples collected by ethologists in a wide range of animals, including primates. The most thoroughly studied instances of such behaviors are those occurring in young birds. Hatchlings arrive in the world with an elaborate set of innate behaviors. First is the complex behavior that allows the young bird to emerge from the egg. Having hatched, a variety of additional behaviors indicate how much of its early life is dependent on inherited information. Hatchlings of precocial species "know" how to preen, peck, gape their beaks, and carry out a variety of other complex acts immediately. In some species, hatchlings automatically crouch down in the nest when a hawk passes overhead but are oblivious to the overflight of an innocuous bird. Konrad Lorenz and Niko Tinbergen used hand-held silhouettes to explore this phenomenon in naïve herring gulls, as illustrated in the figure shown here. "It soon became obvious," wrote Tinbergen, "that … the reaction was mainly one to shape. When the model had a short neck so that the head protruded only a little in front of the line of the wings, it released alarm, independent of the exact shape of the dummy." Evidently, the memory of what the shadow of a predator looks like is built into the nervous system of this species. Examples in primates include the innate fear that newborn monkeys have of snakes and looming objects.

Despite the relatively scant attention paid to this aspect of memory, it is probably the most important component of the stored information in the brain that determines whether or not an individual survives long enough to reproduce.

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fractions of a second. The capacity of immediate memory is very large and each sensory modality (visual, verbal, tactile, and so on) appears to have its own memory register.

Working memory, the second temporal category, is the ability to hold information in mind for seconds to minutes once the present moment has passed. An everyday example of working memory is searching for a lost object; working memory allows the hunt to proceed efficiently, avoiding places already inspected. A conventional way of testing the integrity of working memory at the bedside is to present a string of randomly ordered digits, which the patient is then asked to repeat; surprisingly, the normal "digit span" is only 7–9 numbers.

The third temporal category is **long-term memory** and entails the retention of information in a more permanent form of storage for days, weeks, or even a lifetime. There is general agreement that the so-called **engram**—the physical embodiment of the long-term memory in neuronal machinery—depends on long-term changes in the efficacy of transmission of the relevant synaptic connections, and/or the actual growth and reordering of such connections. As discussed in Chapter 24, there is good reason to think that both these varieties of synaptic change occur.

Evidence for a continual transfer of information from working memory to long-term memory, or **consolidation** (Figure 30.2), is apparent in the phenomenon of **priming**. Priming is typically demonstrated by presenting subjects with a set of items to which they are exposed under false pretenses. For example, a list of words can be given with the instruction that the subjects are to identify some feature that is actually extraneous to the experiment (e.g., whether the words are verbs, adjectives, or nouns). Sometime thereafter (e.g., the next day) the same individuals are given a different test in which they are asked to fill in the missing letters of words with whatever letters come to mind. The test list actually includes fragments of words that were presented in the first test, mixed among fragments of words that were not. Subjects fill in the letters to make the words that were presented earlier at a higher rate than expected by chance, even though they have no specific memory of the words that were seen initially; moreover, they are faster at filling in letters to make words that were seen earlier than new words. Priming shows that information previously presented is influential, even though we are entirely unaware of its effect on subsequent behavior. The significance of priming is well known—at least intuitively—to advertisers, teachers, spouses, and others who want to influence the way we think and act.

Despite the prevalence of such transfer, the information stored in this process is not particularly reliable. Consider, for instance, the list of words in Table 30.1A. If the list is read to a group of students who are immediately asked to identify which of several items were on the original list and which were not (Table 30.1B), the result is surprising. Typically, about half the students report that the word "sweet" was included in the list in Table 30.1A; moreover, they are quite certain about it! The mechanism of such erroneous "recognition" is presumably the strong associations that have previously been made between the words on the list in Table 30.1A and the word "sweet," which bias the students to think that "sweet" was a member of the original set. Clearly, memories, even those we feel quite confident about, are often false.

TABLE 30.1
The Fallibility of Human Memory[a]

(A) Initial list of words	*(B) Subsequent test list*
candy	taste
sour	point
sugar	sweet
bitter	chocolate
good	sugar
taste	nice
tooth	
nice	
honey	
soda	
chocolate	
heart	
cake	
eat	
pie	

[a] After hearing the words in list A read aloud, subjects were asked to identify which of the items in list B had also been on list A. See text for the results.

The Importance of Association in Information Storage

The normal human capacity for remembering relatively meaningless information is surprisingly limited (as noted, a string of about 7–9 numbers or other arbitrary items). This capacity, however, can be increased dramatically. For example, a college student who for some months spent an hour each day practicing the task of remembering randomly presented numbers was able to recall a string of up to about 80 digits (Figure 30.3). He did this primarily

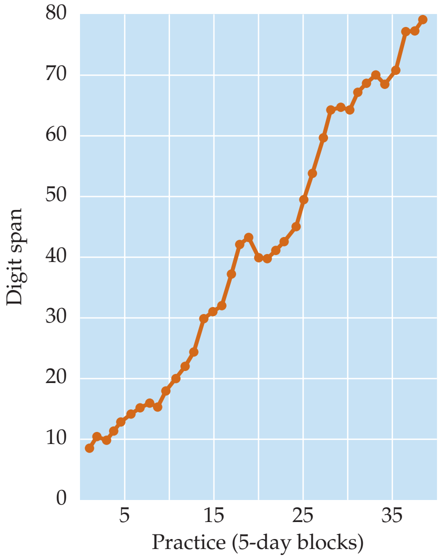
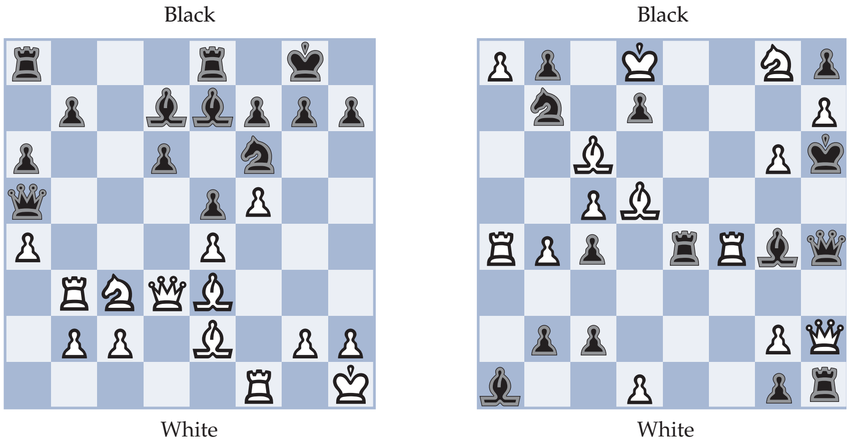
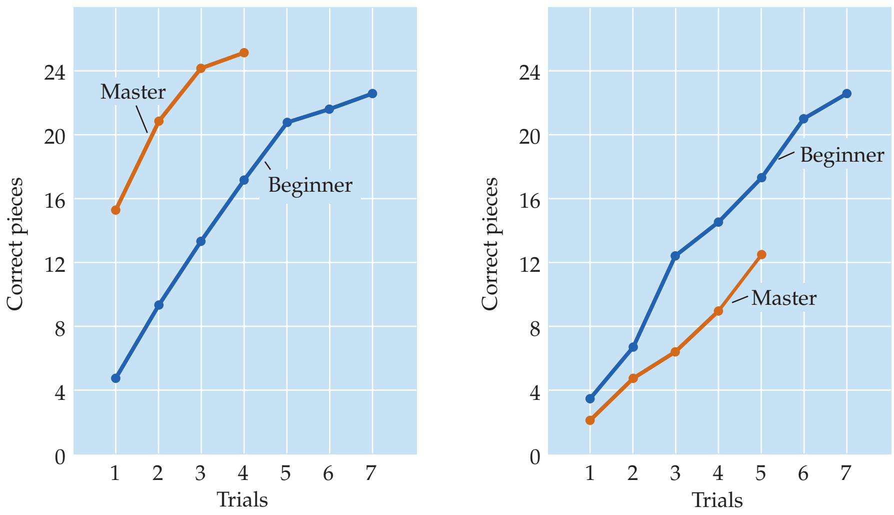


Figure 30.3 Increasing the digit span by practice (and the development of associational strategies). During many months involving one hour of practice a day for 3–5 days a week, this subject increased his digit span from 7 to 79 numbers. Random digits were read to him at the rate of one per second. If a sequence was recalled correctly, one digit was added to the next sequence. (After Ericsson et al., 1980.)

by making subsets of the string of numbers he was given signify dates or times at track meets (he was a competitive runner)—in essence, giving meaningless items a meaningful context. This same strategy of *association* is used by most professional "mnemonists," who amaze audiences by apparently prodigious feats of memory. Similarly, a good chess player can remember the position of many more pieces on a briefly examined board than a poor player, presumably because the positions have much more significance for individuals who know the intricacies of the game than for neophytes (Figure 30.4). Thus, the capacity of working memory very much depends on



(A) (B)



(C) Real game (D) Randomly arranged

Figure 30.4 The retention of briefly presented information depends on past experience, context, and its perceived importance. (A) Board position after white's twenty-first move in game 10 of the 1985 World Chess Championship between A. Karpov (white) and G. Kasparov (black). (B) A random arrangement of the same 28 pieces. (C, D) After briefly viewing the board from the real game, master players reconstruct the positions of the pieces with much greater efficiency than beginning players. With a randomly arranged board, however, beginners perform as well or better than accomplished players. (After Chase and Simon, 1973.)

what the information in question means to the individual and how readily it can be associated with information that has already been stored.

The ability of humans to remember significant information in the normal course of events is, in fact, enormous. Consider Arturo Toscanini, the late conductor of the NBC Philharmonic Orchestra, who allegedly kept in his head the complete scores of more than 250 orchestral works, as well as the music and librettos for some 100 operas. Once, just before a concert in St. Louis, the first bassoonist approached Toscanini in some consternation because he had just discovered that one of the keys on his bassoon was broken. After a minute or two of deep concentration, the story goes, Toscanini turned to the alarmed bassoonist and informed him that there was no need for concern, since that note did not appear in any of the bassoon parts for the evening's program.

A parallel example of a prodigious quantitative memory is the mathematician Alexander Aitken. After an undistinguished career in elementary school, the 13-year-old Aitken was greatly taken with the manipulation of numbers. For the next four years he undertook, as a personal challenge, to master mental calculation. He began by memorizing the value of π to 1000 places, and could soon do calculations in his head with such facility that he became a local celebrity. When asked for the squares of three-digit numbers, he was able to give these almost instantly. The square roots for each were produced to five significant digits in 2–3 seconds; the squares of four-digit numbers allegedly took him about 5 seconds. Aitken went on to become a professor of mathematics at Edinburgh and was eventually elected a Fellow of the Royal Society for his contributions to numerical mathematics, statistics, and matrix algebra. At the age of 30 or so, he began to lose his enthusiasm for "mental yoga," as he called his penchant. In part, his waning enthusiasm stemmed from the realization that the advent of calculators was making his prowess obsolete (it was then 1930). He also discovered that the last 180 digits of π that he had memorized as a boy were wrong; he had taken the values from the published work of another mental calculator, who erred in an era when there was no way to check the correct value. In fact, Aitken's feat has long since been superseded. In 1981, an Indian mnemonist memorized the value of π to 31,811 places, only to have a Japanese mnemonist increase this record to 40,000 places a few years later!

Toscanini's and Aitken's mental processes in these feats were not rote learning, but a result of the fascination that aficionados bring to their special interests (Box B). Although few can boast the mnemonic prowess of such individuals, the human ability to remember the things that deeply interest us—whether baseball statistics, soap opera plots, or the details of brain structure—is amazing.

Forgetting

Some years ago, a poll showed that 84% of psychologists agreed with the statement "everything we learn is permanently stored in the mind, although sometimes particular details are not accessible." The 16% who thought otherwise should get the higher marks. Common sense indicates that, were it not for forgetting, our brains would be impossibly burdened with the welter of useless information that is briefly encoded in our immediate memory "buffer." In fact, the human brain is very good at forgetting. In addition to the unreliable performance on tests such as the example in Table 30.1, Figure 30.5 shows that the memory of the appearance of a penny (an icon seen

Box B

Savant Syndrome

A fascinating developmental anomaly of human memory is seen in rare individuals who until recently were referred to as *idiots savants*; the current literature tends to use the less pejorative phrase *savant syndrome*. Savants are people who, for a variety of poorly understood reasons (typically brain damage in the perinatal period), are severely restricted in most mental activities but extraordinarily competent and mnemonically capacious in one particular domain. The grossly disproportionate skill compared to the rest of their limited mental life can be striking. Indeed, these individuals—whose special talent may be in calculation, history, art, language, or music—are usually diagnosed as severely retarded.

Many examples could be cited, but a summary of one such case suffices to make the point. The individual whose history is summarized here was given the fictitious name "Christopher" in a detailed study carried out by psychologists Neil Smith and Ianthi-Maria Tsimpli. Christopher was discovered to be severely brain damaged at just a few weeks of age (perhaps as the result of rubella during his mother's pregnancy, or anoxia during birth; the record is uncertain in this respect). He had been institutionalized since childhood because he was unable to care for himself, could not find his way around, had poor hand-eye coordination, and a variety of other deficiencies. Tests on standard IQ scales were low, consistent with his general inability to cope with daily life. Scores on the Wechsler Scale were, on different occasions, 42, 67, and 52.

Despite his severe mental incapacitation, Christopher took an intense interest in books from the age of about three, particularly those providing factual information and lists (e.g., telephone directories and dictionaries). At about six or seven he began to read technical papers that his sister sometimes brought home from work, and he showed a surprising proficiency in foreign languages. His special talent in the acquisition and use of language (an area in which savants are often especially limited) grew rapidly. As an early teenager, Christopher could translate from—and communicate in—a variety of languages in which his skills were described as ranging from rudimentary to fluent; these included Danish, Dutch, Finnish, French, German, modern Greek, Hindi, Italian, Norwegian, Polish, Portuguese, Russian, Spanish, Swedish, Turkish, and Welsh. This extraordinary level of linguistic accomplishment is all the more remarkable since he had no formal training in language even at the elementary school level, and could not play tic-tac-toe or checkers because he was unable to grasp the rules needed to make moves in these games.

The neurobiological basis for such extraordinary individuals is not understood. It is fair to say, however, that savants are unlikely to have an ability in their areas of expertise that exceeds the competency of normally intelligent individuals who focus passionately on a particular subject (several examples are given in the text). Presumably, the savant's intense interest in a particular cognitive domain is due to one or more brain regions that continue to work reasonably well. Whether because of social feedback or self-satisfaction, savants clearly spend a great deal of their mental time and energy practicing the skill they can exercise more or less normally. The result is that the relevant associations they make become especially rich, as Christopher's case demonstrates.

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thousands of times since childhood) is uncertain at best, and that people gradually forget what they have seen over the years (TV shows, in this case). Clearly we forget things that have no particular importance, and unused memories deteriorate over time.

The ability to forget unimportant information may be as critical for normal life as retaining information that is significant. One sort of evidence for this presumption is rare individuals who have difficulty with the normal erasure of information. Perhaps the best-known case is a subject studied over several decades by the Russian psychologist A. R. Luria, who referred to the

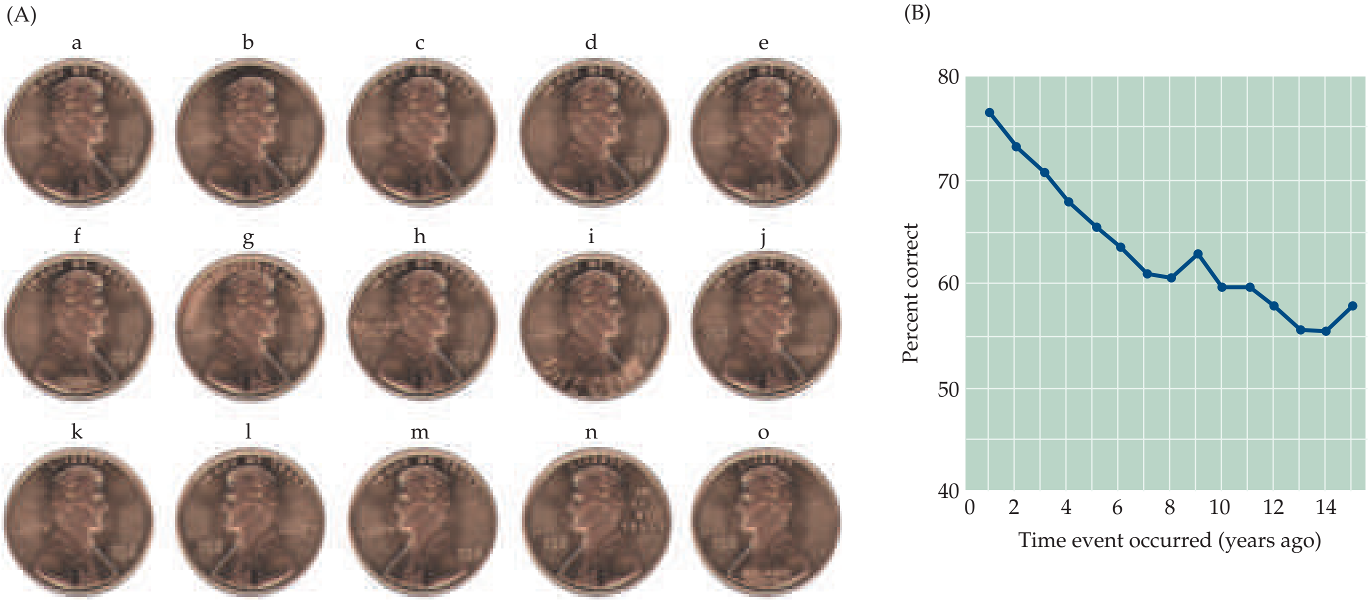

Figure 30.5 Forgetting. (A) Different versions of the "heads" side of a penny. Despite innumerable exposures to this familiar design, few people are able to pick out (a) as the authentic version. Clearly, repeated information is not necessarily retained. (B) The deterioration of long-term memories was evaluated in this example by a multiple-choice test in which the subjects were asked to recognize the names of television programs that had been broadcast for only one season during the past 15 years. Forgetting of stored information that is no longer used evidently occurs gradually and progressively over the years (chance performance = 25%). (A after Rubin and Kontis, 1983; B after Squire, 1989.)

subject simply as "S." Luria's description of an early encounter gives some idea why S, then a newspaper reporter, was so interesting:

> I gave S a series of words, then numbers, then letters, reading them to him slowly or presenting them in written form. He read or listened attentively and then repeated the material exactly as it had been presented. I increased the number of elements in each series, giving him as many as thirty, fifty, or even seventy words or numbers, but this too, presented no problem for him. He did not need to commit any of the material to memory; if I gave him a series of words or numbers, which I read slowly and distinctly, he would listen attentively, sometimes ask me to stop and enunciate a word more clearly, or, if in doubt whether he had heard a word correctly, would ask me to repeat it. Usually during an experiment he would close his eyes or stare into space, fixing his gaze on one point; when the experiment was over, he would ask that we pause while he went over the material in his mind to see if he had retained it. Thereupon, without another moment's pause, he would reproduce the series that had been read to him.
>
> A. R. Luria (1987), *The Mind of a Mnemonist*, pp. 9–10

S's phenomenal memory, however, did not always serve him well. He had difficulty ridding his mind of the trivial information that he tended to focus on, sometimes to the point of incapacitation. As Luria put it:

> Thus, trying to understand a passage, to grasp the information it contains (which other people accomplish by singling out what is most important)

TABLE 30.2
Causes of Amnesia

Causes	*Examples*	*Site of damage*
Vascular occlusion of both posterior cerebral arteries	Patient R.B. (Box C)	Bilateral medial temporal lobe, the hippocampus in particular
Midline tumors	—	Medial thalamus bilaterally (hippocampus and other related structures if tumor is large enough)
Trauma	Patient N.A. (Box C)	Bilateral medial temporal lobe
Surgery	Patient H.M. (Box C)	Bilateral medial temporal lobe
Infections	Herpes simplex encephalitis	Bilateral medial temporal lobe
Vitamin B_1 deficiency	Korsakoff's syndrome	Medial thalamus and mammillary bodies
Electroconvulsive therapy (ECT) for depression	—	Uncertain

> became a tortuous procedure for S, a struggle against images that kept rising to the surface in his mind. Images, then, proved an obstacle as well as an aid to learning in that they prevented S from concentrating on what was essential. Moreover, since these images tended to jam together, producing still more images, he was carried so far adrift that he was forced to go back and rethink the entire passage. Consequently, a simple passage—a phrase, for that matter—would turn out to be a Sisyphean task.
>
> *Ibid.*, p. 113

Although forgetting is a normal and apparently essential mental process, it can also be pathological, a condition called **amnesia**. Some of the causes of memory loss are listed in Table 30.2. An inability to establish new memories following neurological insult is called **anterograde amnesia**, whereas difficulty retrieving memories established prior to the precipitating neuropathology is called **retrograde amnesia**. Anterograde and retrograde amnesia are often present together, but can be dissociated under various circumstances. Amnesias following bilateral lesions of the temporal lobe and diencephalon have given particular insight into where and how at least some categories of memory are formed and stored, as discussed in the next section.

Brain Systems Underlying Declarative Memory Formation

Three extraordinary clinical cases of amnesia have been especially revealing about the brain systems responsible for the short-term storage and consolidation of declarative information and are now familiar to neurologists and psychologists as patients H.M., N.A., and R.B. (Box C). Taken together, these cases provide dramatic evidence of the importance of midline diencephalic and medial temporal lobe structures—the **hippocampus**, in particular—in establishing new declarative memories (Figure 30.6). These patients also demonstrate that there is a different anatomical substrate for anterograde and retrograde amnesia, since in each of these individuals, memory for events *prior* to the precipitating injury was largely retained.

The devastating deficiency is (or was, in the case of R.B.) the inability to establish new memories. Retrograde amnesia—the loss of memory for events preceding an injury or illness—is more typical of the generalized

Box C

Clinical Cases That Reveal the Anatomical Substrate for Declarative Memories

The Case of H.M.

H.M. had suffered minor seizures since age 10 and major seizures since age 16. At the age of 27, he underwent surgery to correct his increasingly debilitating epilepsy. A high school graduate, H.M. had been working as a technician in a small electrical business until shortly before the time of his operation. His attacks involved generalized convulsions with tongue biting, incontinence, and loss of consciousness (all typical of grand mal seizures). Despite a variety of medications, the seizures remained uncontrolled and increased in severity. A few weeks before his surgery, H.M. became unable to work and had to quit his job.

On September 1, 1953, surgeons performed a bilateral medial temporal lobe resection in which the amygdala, uncus, hippocampal gyrus, and anterior two-thirds of the hippocampus were removed. At the time, it was unclear that bilateral surgery of this kind would cause a profound memory defect. Severe amnesia was evident, however, upon H.M.'s recovery from the operation, and his life was changed radically.

The first formal psychological exam of H.M. was conducted nearly 2 years after the operation, at which time a profound memory defect was still obvious. Just before the examination, for instance, H.M. had been talking to the psychologist; yet he had no recollection of this experience a few minutes later, denying that anyone had spoken to him. He gave the date as March 1953 and seemed oblivious to the fact that he had undergone an operation, or that he had become incapacitated as a result. Nonetheless, his score on the Wechsler-Bellevue Intelligence Scale was 112, a value not significantly different from his preoperative IQ. Various psychological tests failed to reveal any deficiencies in perception, abstract thinking, or reasoning; he seemed highly motivated and, in the context of casual conversation, normal. Importantly, he also performed well on tests of the ability to learn new skills, such as mirror writing or puzzle solving (that is, his ability to form procedural memories was intact). Moreover, his early memories were easily recalled, showing that the structures removed during H.M.'s operation are not a permanent repository for such information. On the Wechsler Memory Scale (a specific test of declarative memory), however, he performed very poorly, and he could not recall a preceding test-set once he had turned his attention to another part of the exam. These deficits, along with his obvious inability to recall events in his daily life, all indicate a profound loss of short-term declarative memory function.

During the subsequent decades, H.M. has been studied extensively, primarily by Brenda Milner and her colleagues at the Montreal Neurological Institute. His memory deficiency has continued unabated, and, according to Milner, he has little idea who she is in spite of their acquaintance for nearly 50 years. Sadly, he has gradually come to appreciate his predicament. "Every day is alone," H.M. reports, "whatever enjoyment I've had and whatever sorrow I've had."

The Case of N.A.

N.A. was born in 1938 and grew up with his mother and stepfather, attending public schools in California. After a year of junior college, he joined the Air Force. In October of 1959 he was assigned to the Azores as a radar technician and remained there until December 1960, when a bizarre accident made him a celebrated neurological case.

N.A. was assembling a model airplane in his barracks room while, unbeknownst to him, his roommate was practicing thrusts and parries with a miniature fencing foil behind N.A.'s chair. N.A. turned suddenly and was stabbed through the right nostril. The foil penetrated the cribriform plate (the structure through which the olfactory nerve enters the brain) and took an upward course into the left forebrain. N.A. lost consciousness within a few minutes (presumably because of bleeding in the region of brain injury) and was taken to a hospital. There he exhibited a right-sided weakness and paralysis of the right eye muscles innervated by the third cranial nerve. Exploratory surgery was undertaken and the dural tear repaired. Gradually he recovered and was sent home to California. After some months, his only general neurological deficits were some weakness of upward gaze and mild double vision. He retained, however, a severe anterograde amnesia for declarative memories. MRI studies first carried out in 1986 showed extensive damage to the thalamus and the medial temporal lobe, mostly on the right side; the mammillary bodies also appeared to be missing bilaterally. The exact extent of his lesion, however, is not known, as N.A. remains alive and well.

N.A.'s memory from the time of his injury over 40 years ago to the present has remained impaired and, like H.M., he fails badly on formal tests of new learning ability. His IQ is 124, and he shows no defects in language skills, perception, or other measures of intelligence. He also learns new procedural skills quite normally. His amnesia is not as dense as that of H.M. and is more verbal than spatial. He can, for example, draw accurate diagrams of material presented to him earlier. Nonetheless, he loses track of his possessions, forgets what he has done, and tends to forget who has come to visit him. He has only vague impressions of political, social, and sporting events that have occurred since his injury. Watching television is difficult because he tends to forget the storyline during commercials. On the other hand, his memory for events prior to 1960 is extremely good; indeed, his lifestyle tends to reflect the 1950s.

The Case of R.B.

At the age of 52, R.B. suffered an ischemic episode during cardiac bypass surgery. Following recovery from anesthesia, a profound amnesic disorder was apparent. As in the cases of H.M. and N.A., his IQ was normal (111), and he showed no evidence of cognitive defects other than memory impairment. R.B. was tested extensively for the next five years, and, while his amnesia was not as severe as that of H.M. or N.A., he consistently failed the standard tests of the ability to establish new declarative memories. When R.B. died in 1983 of congestive heart failure, a detailed examination of his brain was carried out. The only significant finding was bilateral lesions of the hippocampus—specifically, cell loss in the CA1 region that extended the full rostral–caudal length of the hippocampus on both sides. The amygdala, thalamus, and mammillary bodies, as well as the structures of the basal forebrain, were normal. R.B.'s case is particularly important because it suggests that hippocampal lesions alone can result in profound anterograde amnesia for declarative memory.

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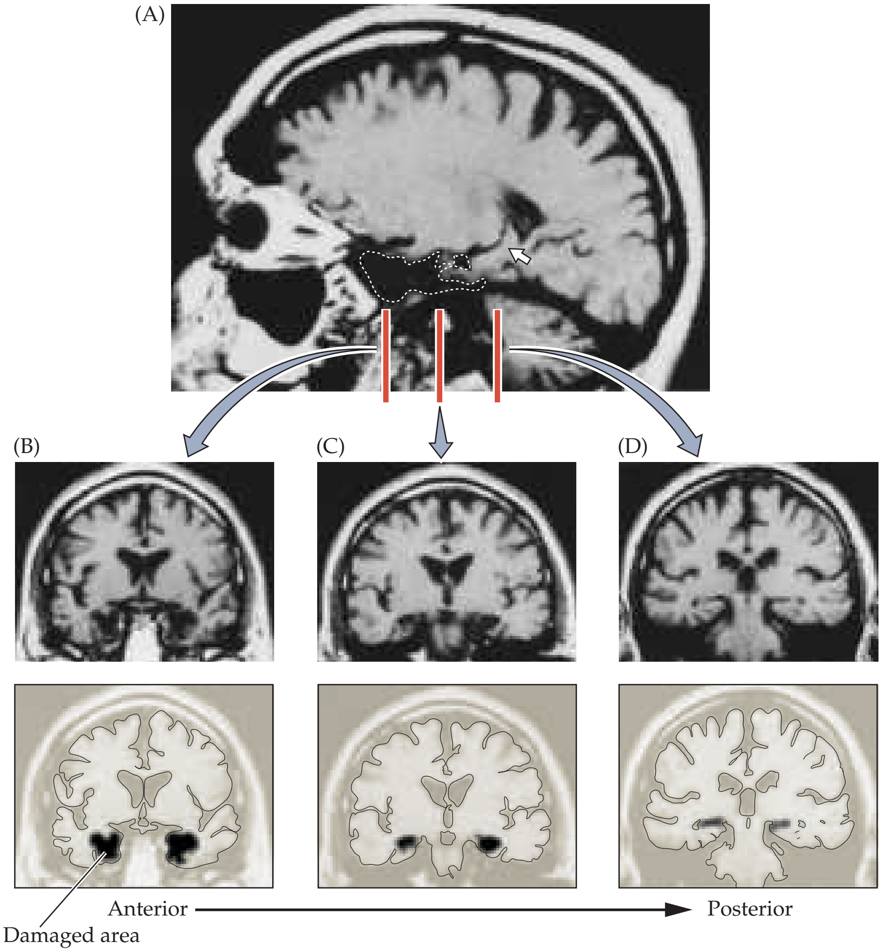
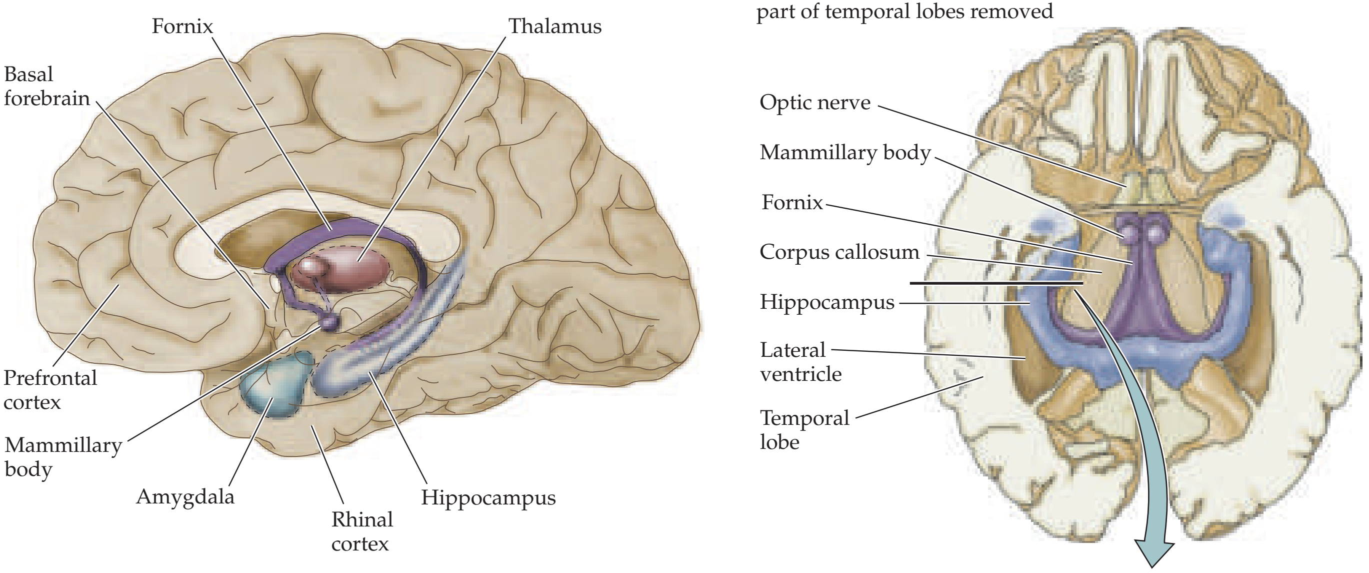


sylvius

MRI images of the brain of patient H.M. (A) Sagittal view of the right hemisphere; the area of the anterior temporal lobectomy is indicated by the white dotted line. The intact posterior hippocampus is the banana-shaped object indicated by the white arrow. (B–D) Coronal sections at approximately the levels indicated by the red lines in (A). Image (B) is the most rostral and is at the level of the amygdala. The amygdala and the associated cortex are entirely missing. Image (C) is at the level of the rostral hippocampus; again, this structure and the associated cortex have been removed. Image (D) is at the caudal level of the hippocampus; the posterior hippocampus appears intact, although somewhat shrunken. Outlines below give a clearer indication of the parts of H.M.'s brain that have been ablated (black shading). (From Corkin et al., 1997.)


(A) Brain areas associated with declarative memory disorders

(B) Ventral view of hippocampus and related structures with part of temporal lobes removed

Fornix
Thalamus
Basal forebrain
Prefrontal cortex
Mammillary body
Amygdala
Rhinal cortex
Hippocampus
Optic nerve
Mammillary body
Fornix
Corpus callosum
Hippocampus
Lateral ventricle
Temporal lobe

(C) Hippocampus in coronal section

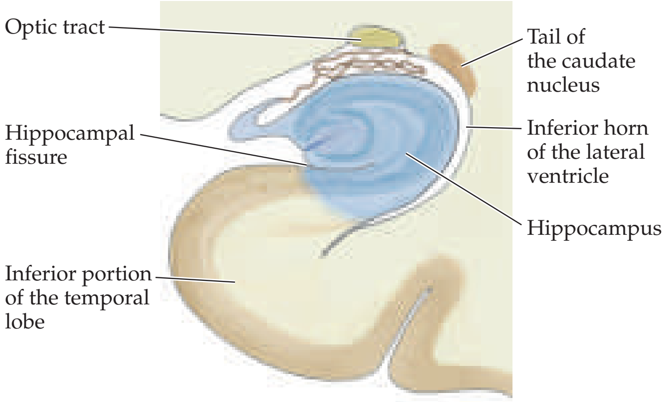
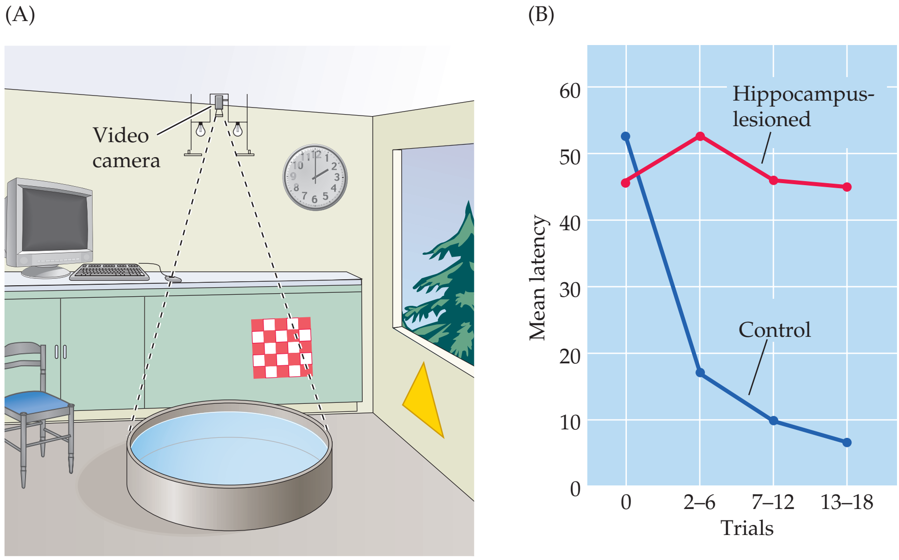

Optic tract
Tail of the caudate nucleus
Hippocampal fissure
Inferior horn of the lateral ventricle
Hippocampus
Inferior portion of the temporal lobe

Figure 30.6 Brain areas that, when damaged, tend to give rise to declarative memory disorders. By inference, declarative memory is based on the physiological activity of these structures. (A) Studies of amnesic patients have shown that the formation of declarative memories depends on the integrity of the hippocampus and its subcortical connections to the mammillary bodies and dorsal thalamus. (B) Diagram showing the location of the hippocampus in a cutaway view in the horizontal plane. (C) The hippocampus as it would appear in a histological section in the coronal plane, at approximately the level indicated by the line in (B).

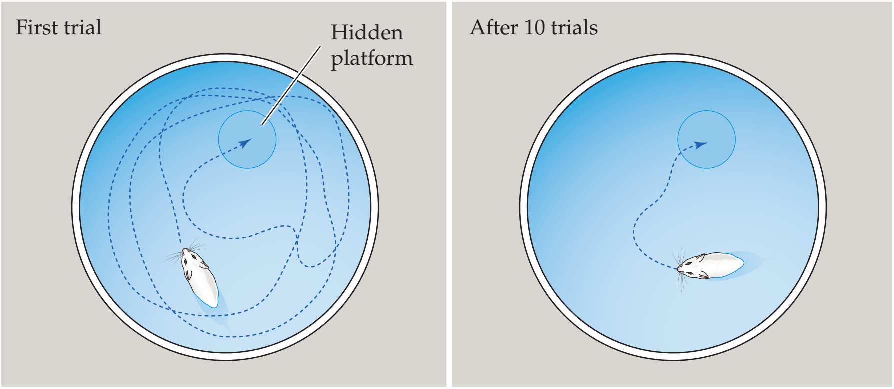
lesions associated with head trauma and neurodegenerative disorders, such as Alzheimer's disease (Box D). Although a degree of retrograde amnesia can occur with the more focal lesions that cause anterograde amnesia, the long-term storage of memories is presumably distributed throughout the brain (see the next section). Thus, the hippocampus and related diencephalic structures indicated in Figure 30.6 form and consolidate declarative memories that are ultimately stored elsewhere.

Other causes of amnesia have also provided some insight into the parts of the brain relevant to various aspects of memory (see Table 30.2). **Korsakoff's syndrome**, for example, occurs in chronic alcoholics as a result of thiamine (vitamin B_1) deficiency. In such cases, loss of brain tissue occurs bilaterally in the mammillary bodies and the medial thalamus, for reasons that are not well understood.

Studies of animals with lesions of the medial temporal lobe have largely corroborated these findings with human patients. For example, one test of the presumed equivalent of declarative memory formation in animals involves placing rats into a pool filled with opaque water, thus concealing a submerged platform; note that the pool is surrounded by prominent visual landmarks (Figure 30.7). Normal rats at first search randomly until they find the submerged platform. After repeated testing, however, they learn to swim directly to the platform no matter where they are initially placed in the pool. Rats with lesions to the hippocampus and nearby structures cannot learn to find the platform, suggesting that remembering the location of the platform



(C) Control rat



(D) Rat with hippocampus lesioned

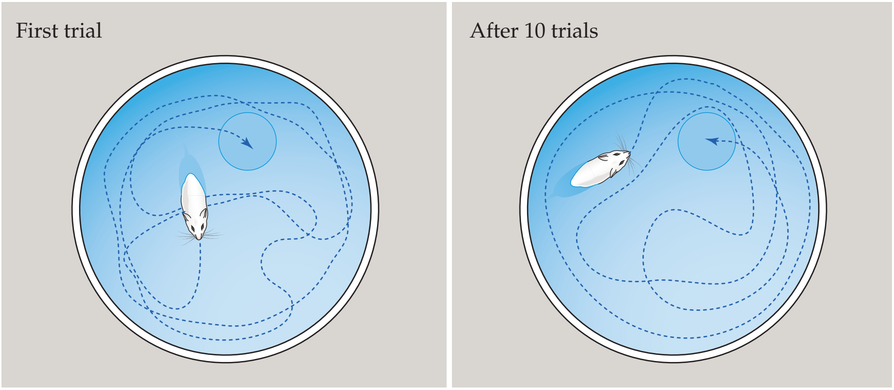


Figure 30.7 Spatial learning and memory in rodents depends on the hippocampus. (A) Rats are placed in a circular tank about the size and shape of a child's wading pool filled with opaque (milky) water. The surrounding environment contains visual cues such as windows, doors, a clock, and so on. A small platform is located just below the surface. As rats search for this resting place, the pattern of their swimming (indicated by the traces in C) is monitored by a video camera. (B) After a few trials, normal rats rapidly reduce the time required to find the platform, whereas rats with hippocampal lesions do not. Sample swim paths of normal rats (C) and hippocampal lesioned rats (D) on the first and tenth trials. Rats with hippocampal lesions are unable to remember where the platform is located (B after Eichenbaum, 2000; C,D after Schenk and Morris, 1985).

relative to the configuration of visual landmarks depends on the same neural structures critical to declarative memory formation in humans. Likewise, destruction of the hippocampus and parahippocampal gyrus in monkeys severely impairs their ability to perform delayed-response tasks (see Figure 25.13). These studies suggest that primates and other mammals depend on medial temporal structures such as the hippocampus and parahippocampal gyrus to encode and consolidate memories of events and objects in time and space, just as humans use these same brain regions for the initial encoding and consolidation of declarative memories.

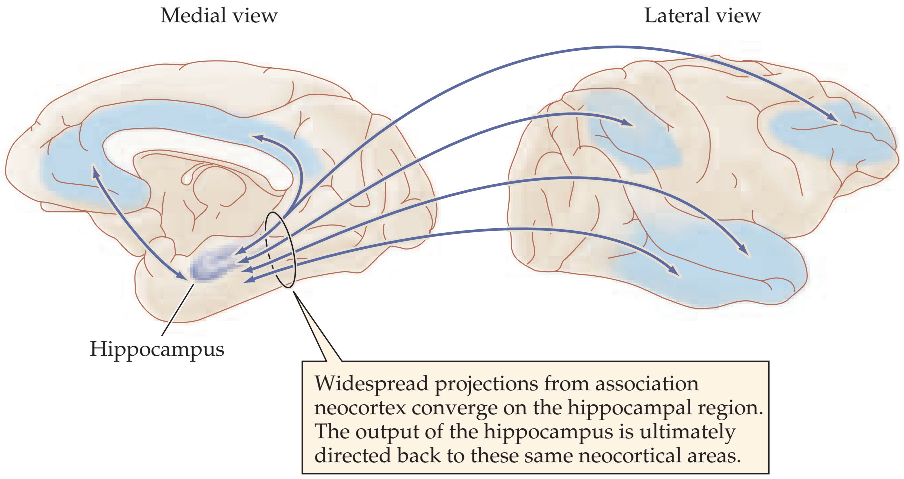
Brain Systems Underlying Long-Term Storage of Declarative Memory

Revealing though they have been, clinical studies of amnesic patients have provided relatively little insight into the long-term storage of declarative information in the brain (other than to indicate quite clearly that such information is *not* stored in the midline diencephalic and medial temporal lobe structures that are affected in anterograde amnesia). Nonetheless, a good deal of evidence implies that the cerebral cortex is the major long-term repository for many aspects of declarative memory.

One line of evidence comes from observations of patients undergoing electroconvulsive therapy (ECT). Individuals with severe depression are often treated by the passage of enough electrical current through the brain to cause the equivalent of a full-blown seizure (this procedure is done under anesthesia, in well-controlled circumstances). This remarkably useful treatment was discovered because depression in epileptics was perceived to remit after a spontaneous seizure (see Box C in Chapter 24). However, ECT often causes both anterograde and retrograde amnesia. Patients typically do not remember the treatment itself or the events of the preceding days, and even their recall of events of the previous 1–3 years can be affected. Animal studies (rats tested for maze learning, for example) have confirmed the amnesic consequences of ECT. The memory loss usually clears over a period of weeks to months. However, to mitigate this side effect (which may be the result of excitotoxicity; see Box B in Chapter 6), ECT is often delivered to only one hemisphere at a time. The nature of amnesia following ECT supports the conclusion that long-term declarative memories are widely stored in the cerebral cortex, since this is the part of the brain predominantly affected by this therapy.

A second line of evidence comes from patients with damage to association cortex outside the medial temporal lobe. Since different cortical regions have different cognitive functions (see Chapters 25 and 26), it is not surprising that these sites store information that reflects the cognitive function of that part of the brain. For example, the lexicon that links speech sounds and their symbolic significance is located in the association cortex of the superior temporal lobe, and damage to this area typically results in an inability to link words and meanings (Wernicke's aphasia; see Chapter 26). Presumably, the widespread connections of the hippocampus to the language areas serve to consolidate declarative information in these and other language-related cortical sites (Figure 30.8). By the same token, the inability of patients with temporal lobe lesions to recognize objects and/or faces suggests that such memories are stored there (see Chapter 25).

A third sort of evidence supporting the hypothesis that declarative memories are stored in cortical areas specialized for processing particular types of



Widespread projections from association neocortex converge on the hippocampal region. The output of the hippocampus is ultimately directed back to these same neocortical areas.

Figure 30.8 Connections between the hippocampus and possible declarative memory storage sites. The rhesus monkey brain is shown because these connections are much better documented in non-human primates than in humans. Projections from numerous cortical areas converge on the hippocampus and the related structures known to be involved in human memory; most of these sites also send projections to the same cortical areas. Medial and lateral views are shown, the latter rotated 180° for clarity. (After Van Hoesen, 1982.)

information comes from neuroimaging of human subjects recalling vivid memories. In one such study, subjects first examined words paired with either pictures or sounds. Their brains were then scanned while they were asked to recall whether each test word was associated with either a picture or a sound. Functional images based on these scans showed that the cortical areas activated when subjects viewed pictures or heard sounds were reactivated when these percepts were vividly recalled. In fact, this sort of reactivation can be quite specific. Thus, different classes of visual images—such as faces, houses, or chairs—tend to reactivate the same small regions of the visual association cortex that were activated when the objects were actually perceived (Figure 30.9).

These neuroimaging studies reinforce the conclusion that declarative memories are stored widely in specialized areas of the cerebral cortex. Retrieving such memories appears to involve the medial temporal lobe, as well as regions of the frontal cortex. Frontal cortical areas located on the dorsolateral and anterolateral aspect of the brain, in particular, are activated when normal subjects attempt to retrieve declarative information from long-term memory. Moreover, patients with damage to these areas often fail to accurately recall the details of a memory and sometimes resort to confabulation to fill in the missing information. Finally, whereas the ability of patients such as H.M., N.A., and R.B. to remember facts and events from the period of their lives preceding their lesions clearly demonstrates that the medial temporal lobe is not necessary for retrieving declarative information held in long-term memory, other studies have suggested that these structures may be important for recalling declarative memories during the early stages of consolidation and storage in the cerebral cortex.

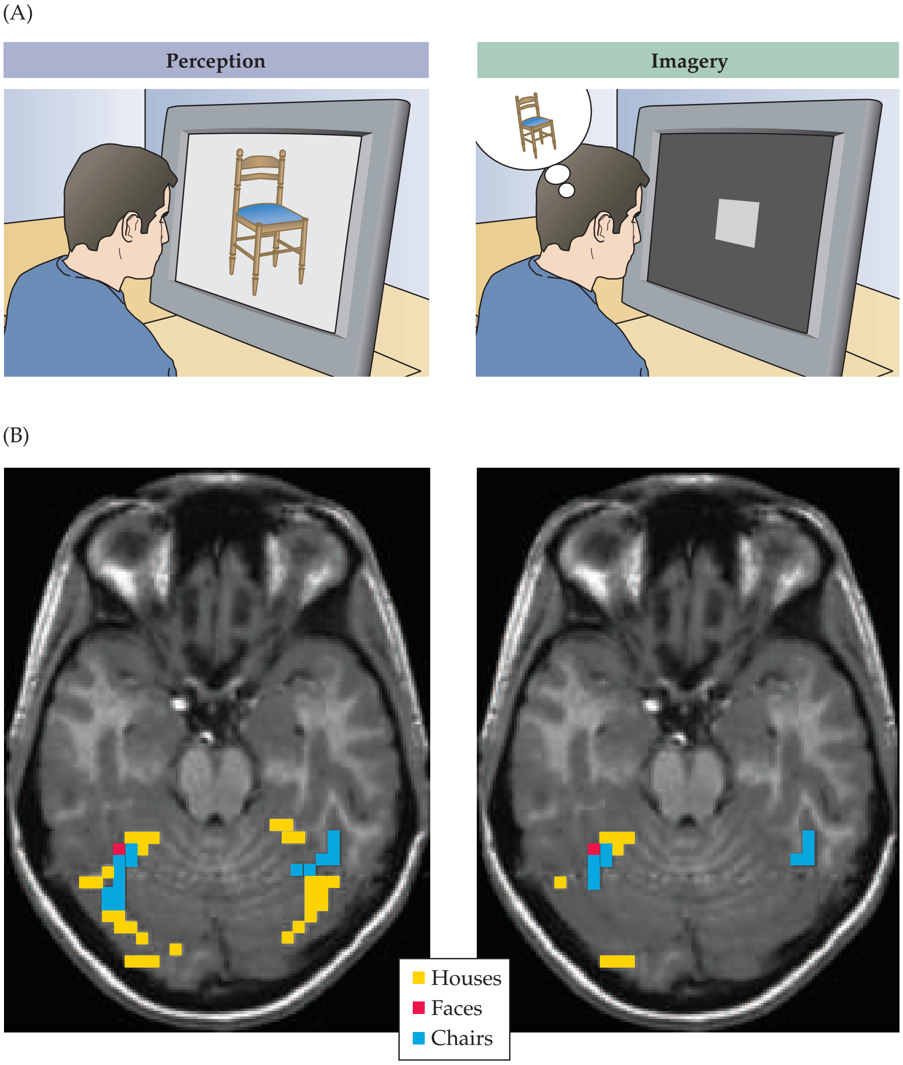


Figure 30.9 Reactivation of visual cortex during vivid remembering of visual view images. (A) Subjects were instructed to view either images of objects (houses, faces, and chairs) (left) or imagine the objects in the absence of the stimulus (right). (B) (Left) Bilateral regions of ventral temporal cortex are specifically activated during perception of houses (yellow), faces (red), and chairs (blue). (Right) When subjects recall these objects, the same regions preferentially activated during the perception of each object class are reactivated. (After Ishai et al., 2000).

Brain Systems Underlying Nondeclarative Learning and Memory

H.M., N.A., and R.B. had no difficulty establishing or recalling nondeclarative memories, indicating that this information is laid down by using an anatomical substrate different from that used in declarative memory formation. Nondeclarative memory apparently involves the basal ganglia, prefrontal cortex, amygdala, sensory association cortex, and cerebellum, but not the medial temporal lobe or midline diencephalon. In support of this interpretation, perceptual priming (the influence of previously studied information on subsequent performance, unavailable to conscious recall) depends critically on the integrity of sensory association cortex. For example, lesions of the visual association cortex produce profound impairments in visual priming but leave declarative memory formation intact. Likewise, simple sensory-motor conditioning, such as learning to blink following a tone that predicts a puff of air directed at the eye, relies on the normal activation of neural circuits in the cerebellum. Ischemic damage to the cerebellum following infarcts of the superior cerebellar artery or the posterior inferior cerebellar artery cause profound deficits in classical eyeblink conditioning without interfering with the

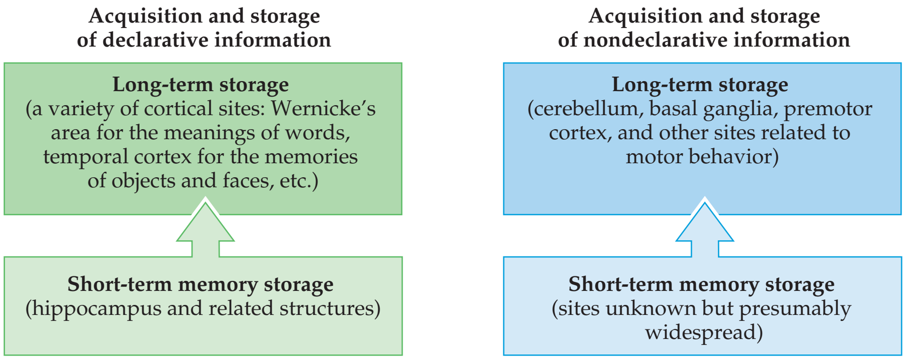

Acquisition and storage of declarative information
Long-term storage (a variety of cortical sites: Wernicke's area for the meanings of words, temporal cortex for the memories of objects and faces, etc.)
Short-term memory storage (hippocampus and related structures)
Acquisition and storage of nondeclarative information
Long-term storage (cerebellum, basal ganglia, premotor cortex, and other sites related to motor behavior)
Short-term memory storage (sites unknown but presumably widespread)

Figure 30.10 Summary diagram of the acquisition and storage of declarative versus nondeclarative information.

ability to lay down new declarative memories. Evidence from such double-dissociations endorses the idea that independent brain systems govern the formation and storage of declarative and nondeclarative memories.

A brain system that appears to be especially important for complex motor learning involves the signaling loops that connect the basal ganglia and prefrontal cortex (see Chapter 17). Damage to either structure profoundly interferes with the ability to learn new motor skills. Thus, patients with Huntington's disease, which causes atrophy of the caudate and putamen (see Figure 17.9B), perform poorly on motor skill learning tests such as manually tracking a spot of light, tracing curves using a mirror, or reproducing sequences of finger movements. Because the loss of dopaminergic neurons in the substantia nigra interferes with normal signaling in the basal ganglia (see Figure 17.9A), patients with Parkinson's disease show similar deficits in motor skill learning, as do patients with prefrontal lesions caused by tumors or strokes. Neuroimaging studies have largely corroborated these findings, revealing activation of the basal ganglia and prefrontal cortex in normal subjects performing these same skill-learning tests. Activation of the basal ganglia and prefrontal cortex has also been observed in animals carrying out rudimentary motor learning and sequencing tasks.

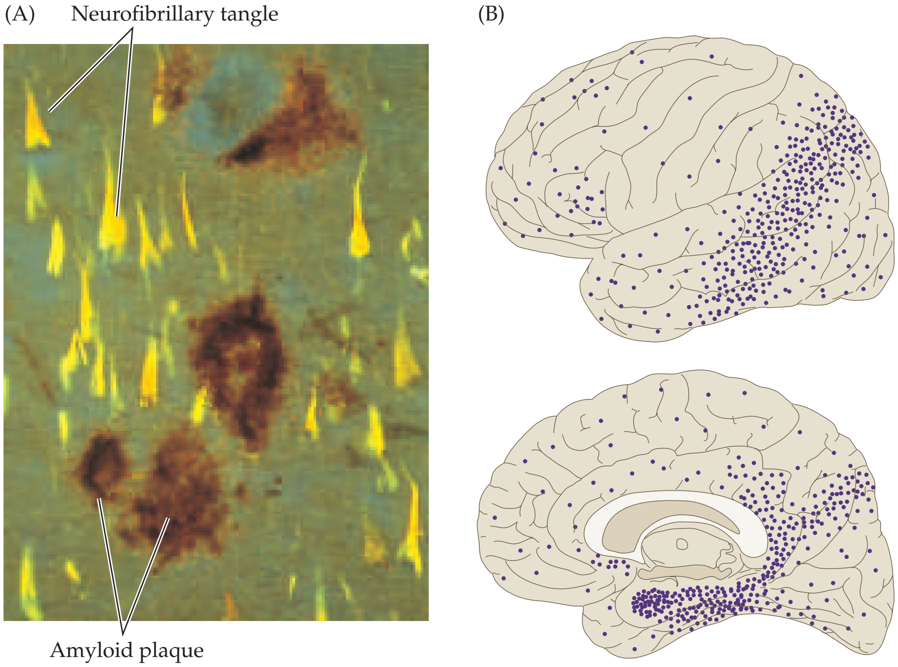
The dissociation of memory systems supporting declarative and nondeclarative memory suggests the scheme for long-term information storage diagrammed in Figure 30.10. The generality of the diagram only emphasizes the rudimentary state of present thinking about exactly how and where long-term memories are stored. A reasonable guess is that each complex memory is instantiated in an extensive network of neurons whose activity depends on synaptic weightings that have been molded and modified by experience.

Memory and Aging

Although it is all too obvious that our outward appearance changes with age, we tend to imagine that the brain is much more resistant to the ravages of time. Unfortunately, the evidence suggests that this optimistic view is not justified. From early adulthood onward, the average weight of the normal human brain, as determined at autopsy, steadily decreases (Figure 30.11). In elderly individuals, this effect can also be observed with noninvasive imaging as a slight but nonetheless significant shrinkage of the brain. Counts of synapses in the cerebral cortex generally decrease in old age (although the number of neurons probably does not change very much), suggesting that it is mainly the connections between neurons (i.e., neuropil) that are lost as

Box D
Alzheimer's Disease

Dementia is a syndrome characterized by failure of recent memory and other intellectual functions that is usually insidious in onset but steadily progresses. Alzheimer's disease (AD) is the most common dementia, accounting for 60–80% of cases in the elderly. It afflicts 5–10% of the population over the age of 65, and as much as 45% of the population over 85. The earliest sign is typically an impairment of recent memory function and attention, followed by failure of language skills, visual–spatial orientation, abstract thinking, and judgment. Inevitably, alterations of personality accompany these defects.



(A) Histological section of the cerebral cortex from a patient with Alzheimer's disease, showing characteristic amyloid plaques and neurofibrillary tangles. (B) Distribution of pathologic changes (including plaques, tangles, neuronal loss, and gray matter shrinkage) in Alzheimer's disease. Dot density indicates severity of pathology. (A from Roses, 1995, courtesy of Gary W. Van Hoesen; B after Blumenfeld, 2002, based on Brun and Englund, 1981.)

The tentative diagnosis of Alzheimer's disease is based on these characteristic clinical features, and can only be confirmed by the distinctive cellular pathology evident on postmortem examination of the brain. The histopathology consists of three principal features (illustrated in the figure): (1) collections of intraneuronal cytoskeletal filaments called *neurofibrillary tangles*; (2) extracellular deposits of an abnormal protein in a matrix called amyloid in so-called *senile plaques*; and (3) a diffuse loss of neurons. These changes are most apparent in neocortex, limbic structures (hippocampus, amygdala, and their associated cortices), and selected brainstem nuclei (especially the basal forebrain nuclei).

Although the vast majority of AD cases arise sporadically, the disorder is inherited in an autosomal dominant pattern in a small fraction (less than 1%) of patients. Identification of the mutant gene in a few families with an early-onset autosomal dominant form of the disease has provided considerable insight into the kinds of processes that go awry in Alzheimer's.

Investigators suspected that the mutant gene responsible for familial AD might reside on chromosome 21, primarily because similar clinical and neuropathologic features often occur in individuals with Down's syndrome (a syndrome typically caused by an extra copy of chromosome 21), but with a much earlier onset (at about age 30 in most cases). The prominence of amyloid deposits in AD further suggested that a mutation of a gene encoding amyloid precursor protein is somehow involved. The gene for amyloid precursor protein (APP) was cloned by D. Goldgaber and colleagues, and found to reside on chromosome 21. This discovery eventually led to the identification of mutations of the *APP* gene in almost 20 families with the early-onset autosomal dominant form of AD. It should be noted, however, that only a few of the early-onset families, and none of the late-onset families, exhibited these particular mutations. The mutant genes underlying two additional autosomal dominant forms of AD have been subsequently identified (*presenilin 1* and *presenilin 2*). Thus, mutation of any one of several genes appears to be sufficient to cause a heritable form of AD.

The most common form of Alzheimer's occurs late in life, and although the relatives of affected individuals are at a greater risk, the disease is clearly not inherited in any simple sense. The central role of APP in the families with the early-onset form of the disease nonetheless suggested that APP might be linked to the chain of events culminating in the "spontaneous" forms of Alzheimer's disease. In particular, biochemists Warren Strittmatter and Guy Salvesen theorized that pathologic deposition of proteins complexed with a derivative of APP might be responsible. To test this idea, they immobilized a recombinant form of the APP derivative on nitrocellulose paper and searched for proteins in the cerebrospinal fluid of patients with Alzheimer's disease that bound with high affinity. One of the proteins they detected was apolipoprotein E (ApoE), a molecule that normally chaperones cholesterol through the bloodstream.

This discovery was especially provocative in light of a discovery made by Margaret Pericak-Vance, Allen Roses, and their colleagues at Duke University Medical Center, who found that affected members of some families with the late-onset form of the inherited disease exhibited an association with genetic markers on chromosome 19. This finding was of particular interest because a gene encoding an isoform of apolipoprotein E (the *ε4* allele) is located in the same region of chromosome 19 implicated by the family studies. As a result, they began to explore the association of the different alleles of apolipoprotein E with affected members in families with a late-onset but inherited form of Alzheimer's disease.

There are three major alleles of apolipoprotein E, *ε2*, *ε3*, and *ε4*. The frequency of allele *ε3* in the general population is 0.78, and the frequency of allele *ε4* is 0.14. The frequency of the ε4 allele in late-onset familial AD patients, however, is 0.52—almost 4 times higher than the general population. Thus, the inheritance of the *ε4* allele is a risk factor for late-onset AD. In fact, people homozygous for *ε4* are about 8 times more likely to develop AD compared to individuals homozygous for ε3. Among individuals in late-onset Alzheimer's families with no copies of *ε4*, only 20% develop AD by age 75 compared to 90% of individuals with two copies of *ε4*. An increased association of the *ε4* allele has also been shown in the sporadic form of AD, an especially important discovery because this category constitutes by far the most common form of the disease.

It is not known whether the ε4 allele of ApoE itself is responsible for the increased risk, or whether it is linked to another gene on chromosome 19 that is the real culprit. The fact that ApoE binds avidly to amyloid plaques in AD brains favors the idea that the *ε4* allele of ApoE itself is the problem. However, in contrast to the mutations of *APP* or *presenilin 1* and *presenilin 2* that cause familial forms of AD, inheriting the *ε4* form of ApoE is *not* sufficient to cause AD; rather, inheriting this gene simply increases the risk of developing AD. Moreover, some of the individuals with early-onset forms of familial AD do not have the *ε4* allele. Thus, a variety of related molecular anomalies appear to underlie AD.

A possible common denominator of AD at the cellular level is the "amyloid cascade" hypothesis. A prominent constituent of the amyloid plaques is an abnormal cleavage product of APP called amyloid-β peptide (or β-A4). The cascade hypothesis proposes that accumulation of β-A4 is critical to the pathogenesis of AD. Others, however, argue that extracellular deposition of β-A4 may not be a key event in the pathogenesis of AD because the density of the β-A4 plaques correlates only poorly with severity of the dementia (the degree of dementia being much better correlated with the density of neurofibrillary tangles). Moreover, a transgenic mouse model of AD based on a *presenilin 1* mutation exhibits neurodegeneration without amyloid plaque formation.

Clearly, AD has a complex pathology and probably reflects a variety of related molecular and cellular abnormalities. It is unlikely that this important problem will be understood without a great deal more research, much hyperbole in the lay press notwithstanding.

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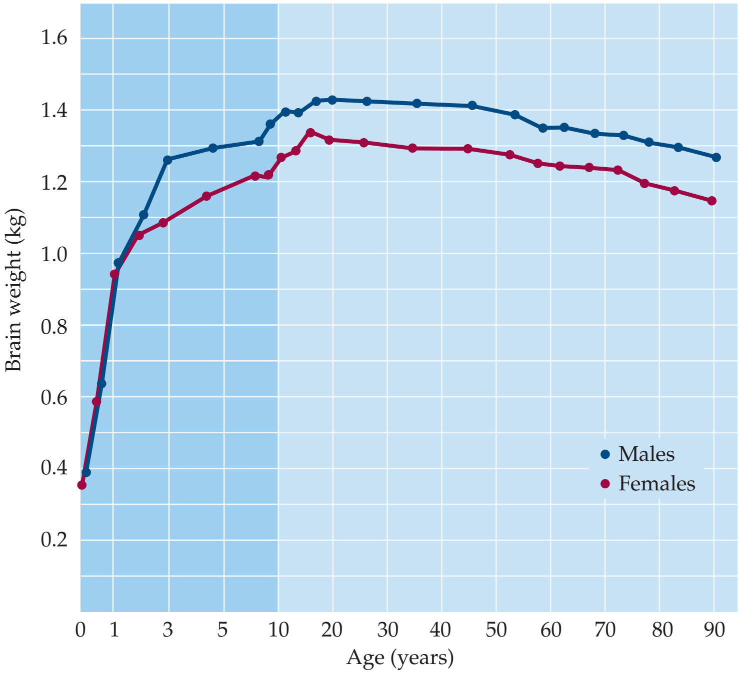
Figure 30.11 Brain size as a function of age. The human brain reaches its maximum size (measured by weight in this case) in early adult life and decreases progressively thereafter. This decrease evidently represents the gradual loss of neural circuitry in the aging brain, which presumably underlies the progressively diminished memory function in older individuals. (After Dekaban and Sadowsky, 1978.)

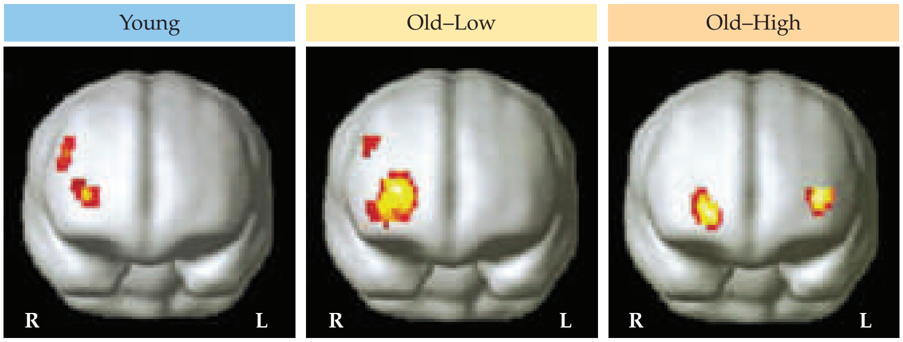


humans grow old (consistent with the idea that the networks of connections that represent memories—i.e., the engrams—gradually deteriorate).

These several observations accord with the difficulty older people have in making associations (e.g., remembering names or the details of recent experiences) and with declining scores on tests of memory as a function of age. The normal loss of some memory function with age means that there is a large gray zone between individuals undergoing normal aging and patients suffering from age-related dementias such as Alzheimer's disease (see Box D).

Just as regular exercise slows the deterioration of the neuromuscular system with age, age-related neurodegeneration and associated cognitive decline may be slowed in elderly individuals who make a special effort to continue using the full range of human memory abilities (i.e, both declarative and nondeclarative memory tasks). Although cognitive decline with age is ultimately inevitable, neuroimaging studies suggest that high-performing older adults may to some degree offset declines in processing efficacy through compensatory activation of cortical tissue that is less fully used during remembering in poorly performing older adults (Figure 30.12).

Figure 30.12 Compensatory activation of memory areas in high-functioning older adults. During remembering, activity in prefrontal cortex was restricted to the right prefrontal cortex (following radiological conventions, the brain images are left-right reversed) in both young participants and elderly subjects with poor recall. In contrast, elderly subjects with relatively good memory showed activation in both right and left prefrontal cortex. (After Cabeza et al., 2002).



Summary

Human memory entails a number of biological strategies and anatomical substrates. Primary among these are a system for memories that can be expressed by means of language and can be made available to the conscious mind (declarative memory), and a separate system that concerns skills and associations that are essentially prelinguistic, operating at a largely unconscious level (nondeclarative or procedural memory). Based on evidence from amnesic patients and knowledge about normal patterns of neural connections in the human brain, the hippocampus and associated midline diencephalic and medial temporal lobe structures are critically important in laying down new declarative memories, although not in storing them (a process that occurs primarily in the association cortices). In contrast, nondeclarative memories for motor and other unconscious skills depends on the integrity of the premotor cortex, basal ganglia, and cerebellum, and is not affected by lesions that impair the declarative memory system. The common denominator of these categories of stored information is generally thought to be alterations in the strength and number of the synaptic connections in the cerebral cortices that mediate associations between stimuli and the behavioral responses to them.

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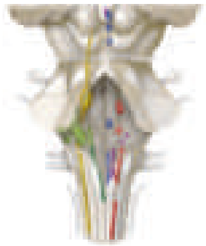
Appendix A



The Brainstem and Cranial Nerves

The brainstem, comprising the midbrain, pons, and medulla, is continuous rostrally with the diencephalon (thalamus and hypothalamus) and with the spinal cord caudally. Although the medulla, pons, and midbrain participate in myriad specific functions, the integrated actions of these brainstem components give rise to three fundamental functions. First, the brainstem is the target or source for the cranial nerves that deal with sensory and motor function in the head and neck (Figure A1; Table A1). Second, the brainstem provides a "thruway" for all of the ascending sensory tracts from the spinal cord; the sensory tracts for the head and neck (the **trigeminal system**); the descending motor tracts from the forebrain; and local pathways that link eye movement centers. Finally, the brainstem is involved in regulating the level of consciousness, primarily though the extensive forebrain projections of a portion of the brainstem core, the **reticular formation** (see Box A in Chapter 16).

Understanding the internal anatomy of the brainstem is generally regarded as essential for the practice of clinical medicine. Brainstem structures are compressed into a relatively small volume that has a regionally restricted vascular supply (see Appendix B, Figure B7). Thus, vascular accidents in the brainstem—which are common—result in distinctive, and often devastating, combinations of functional deficits (see Appendix B, Box A). These deficits can be used both for diagnosis and for better understanding of the intricate anatomy of the medulla, pons, and midbrain.

Unlike the spinal cord, which is relatively homogeneous in appearance along its length, the surface appearance of each brainstem subdivision is characterized by unique bumps and bulges formed by the underlying gray matter (nuclei) or white matter (tracts) (Figures A1 and A2). The **midbrain** contains the **superior** and **inferior colliculi** defining its dorsal surface, or tectum (meaning "roof"). Several midbrain nuclei, including the **substantia nigra**, lie in the ventral portion or tegmentum (meaning "covering") of the midbrain. The other noteworthy anatomical feature of the midbrain is the presence of the prominent **cerebral peduncles** that are visible from the ventral surface.

The **pons** is caudal to the midbrain and is easily recognized by the mass of decussating fibers on its ventral surface that give this subdivison its name; *pons* literally means "bridge." The **cerebellum** is attached to the dorsal aspect of the pons by three large white matter tracts, the **superior, middle** and **inferior cerebellar peduncles**. Each of these tracts contains either efferent (superior) or afferent (inferior and middle) axons from or to the cerebellum.

There is a series of swellings on the dorsal and ventral surfaces of the medulla that reflect many of the major structures in this part of the brainstem. Laterally, the **inferior olivary complex** can be seen. Adjacent and

TABLE A1
The Cranial Nerves and Their Primary Functions

Cranial nerve	*Name*	*Sensory and/or motor*	*Major function*
I	Olfactory nerve	Sensory	Sense of smell
II	Optic nerve	Sensory	Vision
III	Oculomotor nerve	Motor	Eye movements; papillary constriction and accommodation; muscles of eyelid.
IV	Trochlear nerve	Motor	Eye movements
V	Trigeminal nerve	Sensory and motor	Somatic sensation from face, mouth, cornea; muscles of mastication
VI	Abducens nerve	Motor	Eye movements
VII	Facial nerve	Sensory and motor	Controls the muscles of facial expression; taste from anterior tongue; lacrimal and salivary glands
VIII	Vestibulocochlear (auditory) nerve	Sensory	Hearing; sense of balance
IX	Glossopharyngeal nerve	Sensory and motor	Sensation from pharynx; taste from posterior tongue; carotid baroreceptors
X	Vagus nerve	Sensory and motor	Autonomic functions of gut; sensation from pharynx; muscles of vocal cords; swallowing
XI	Spinal accessory nerve	Motor	Shoulder and neck muscles
XII	Hypoglossal nerve	Motor	Movements of tongue

slightly medial to the olivary complex are ridges that represent the vagal and hypoglossal nuclei. The **pyramids** are prominent swellings on the ventral surface of the medulla, reflecting the underlying descending corticospinal tract (see Figure 16.8).

The surface features of the midbrain, pons, and medulla can be used as landmarks for locating the source and termination of the majority of cranial nerves in the brainstem. Unlike the spinal nerves, the entry and exit points of the cranial nerves are not regularly arrayed along the length of the brainstem. Two cranial nerves, the **olfactory nerve (I)** and the **optic nerve (II)**, enter the forebrain directly. The remaining cranial nerves enter and exit at distinct regions of the ventral (and in one case, the dorsal) surface of the midbrain, pons, and medulla (Figure A1). The **oculomotor nerve (III)** exits into the space between the two cerebral peduncles on the ventral surface of the midbrain. The **trochlear nerve (IV)** associated with the caudal midbrain is the only cranial nerve to exit on the dorsal surface of the brainstem. The **trigeminal nerve (V)**—the largest cranial nerve—exits the ventrolateral pons through the middle cerebellar peduncle. The **abducens nerve (VI)**, **facial nerve (VII)**, and **vestibulocochlear nerve (VIII)** emerge in a medial to lateral manner, respectively, at the junction of the pons and medulla. The **glossopharyngeal nerve (IX)** and the **vagus nerve (X)** are associated with the lateral medulla, whereas the **hypoglossal nerve (XII)** exits the ventromedial medulla between the pyramids and the inferior olive. The **spinal accessory nerve (XI)** does not originate in the brainstem but, as its name implies, exits the lateral portion of the upper cervical spinal cord. Table A1 describes the major functions of the cranial nerves.

Location of cells whose axons form the nerve	*Clinical test of function*
Nasal epithelium	Test sense of smell with standard odor
Retina	Measure acuity and integrity of visual field
Oculomotor nucleus in midbrain; Edinger-Westphal nucleus in midbrain	Test eye movements (patient can't look up, down, or medially if nerve involved); look for ptosis, pupillary dilation
Trochlear nucleus in midbrain	Can't look downward when eye abducted
Trigeminal motor nucleus in pons; trigeminal sensory ganglion (the gasserian ganglion)	Test sensation on face; palpate masseter muscles and temporal muscle
Abducens nucleus in midbrain	Can't look laterally
Facial motor nucleus; superior salivatory nuclei in pons; trigeminal (gasserian) ganglion	Test facial expression plus taste on anterior tongue
Spiral ganglion; vestibular (Scarpa's) ganglion	Test audition with tuning fork; vestibular function with caloric test
Nucleus ambiguus; inferior salivatory	Test swallowing; pharyngeal gag reflex
Dorsal motor nucleus of vagus; vagal nerve ganglion	Test above plus hoarseness
Spinal accessory nucleus; nucleus ambiguus; intermediolateral column of spinal cord	Test sternocleidomastoid and trapezius muscles
Hypoglossal nucleus of medulla	Test deviation of tongue during protrusion (points to side of lesion)

Cranial nerve nuclei within the brainstem are the targets of cranial sensory nerves or the source of cranial motor nerves (Figure A2; Table A2). Cranial nerve nuclei that receive sensory input (analogous to the dorsal horns of the spinal cord) are located separately from those that give rise to motor output (which are analogous to the ventral horns). The primary sensory neurons that innervate these nuclei are found in ganglia associated with the cranial nerves—similar to the relationship between dorsal root ganglia and the spinal cord. In general, sensory nuclei are found laterally in the brainstem, whereas motor nuclei are located more medially (Figure A3). There are three types of brainstem motor nuclei: **somatic motor nuclei** project to striated muscles; **branchial motor nuclei** project to muscles derived from embryonic structures called branchial arches (these arches give rise to the muscles—and bones—of the jaws and other cranio-facial structures); and **visceral motor nuclei** project to peripheral ganglia that innervate smooth muscle or glandular targets, similar to preganglionic motor neurons in the spinal cord that innervate autonomic ganglia. Finally, the major ascending or descending tracts—carrying sensory or motor information to or from the brain—are found in the lateral and basal regions of the brainstem (Figure A3).

The rostral–caudal organization of the cranial nerve nuclei (all of which are bilaterally symmetric) reflects the rostrocaudal distribution of head and neck structures (see Figure A2 and Tables A1 and A2). The more caudal the nucleus, the more caudally located the target structures in the periphery. For example, the spinal accessory nucleus in the cervical spinal cord and caudal medulla provides motor innervation for neck and shoulder muscles, and the motor nucleus of the vagus nerve provides preganglionic innervation for

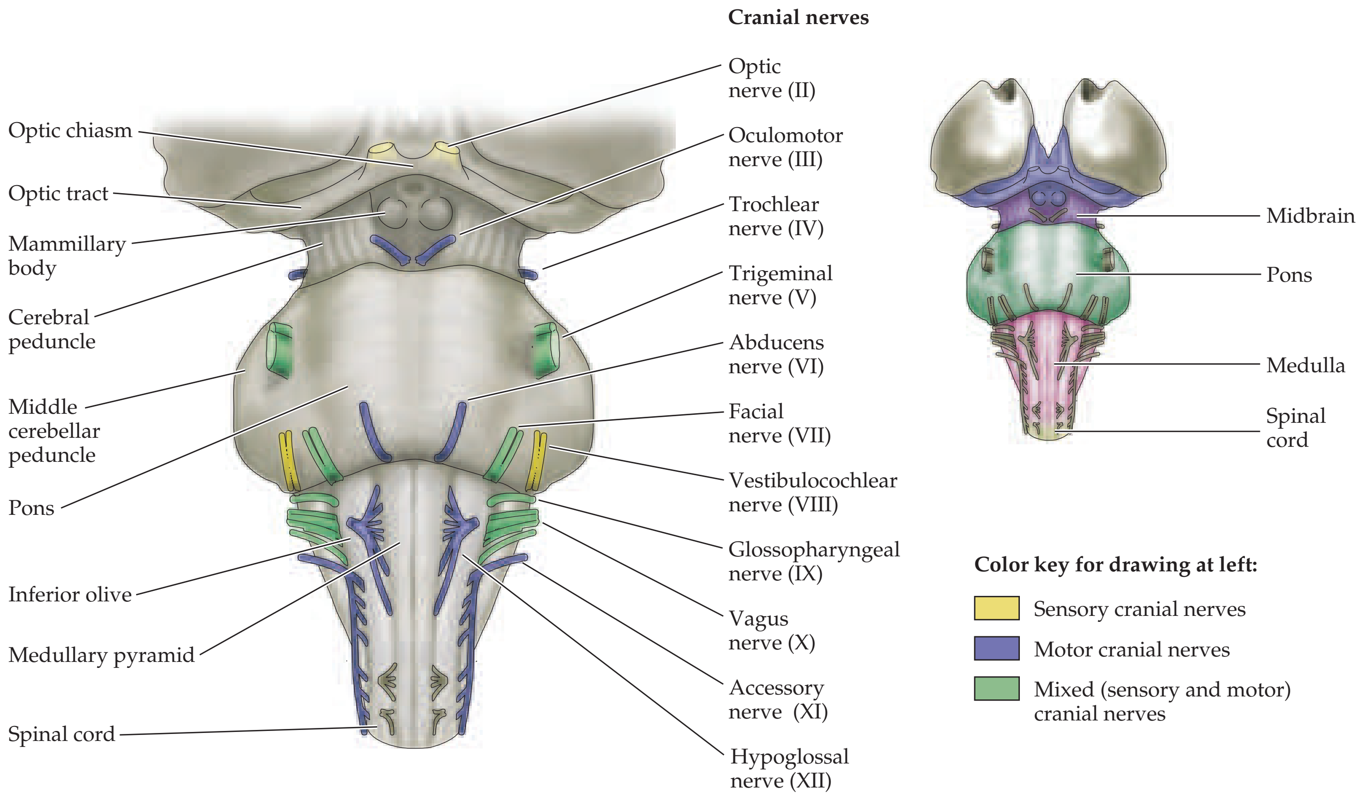
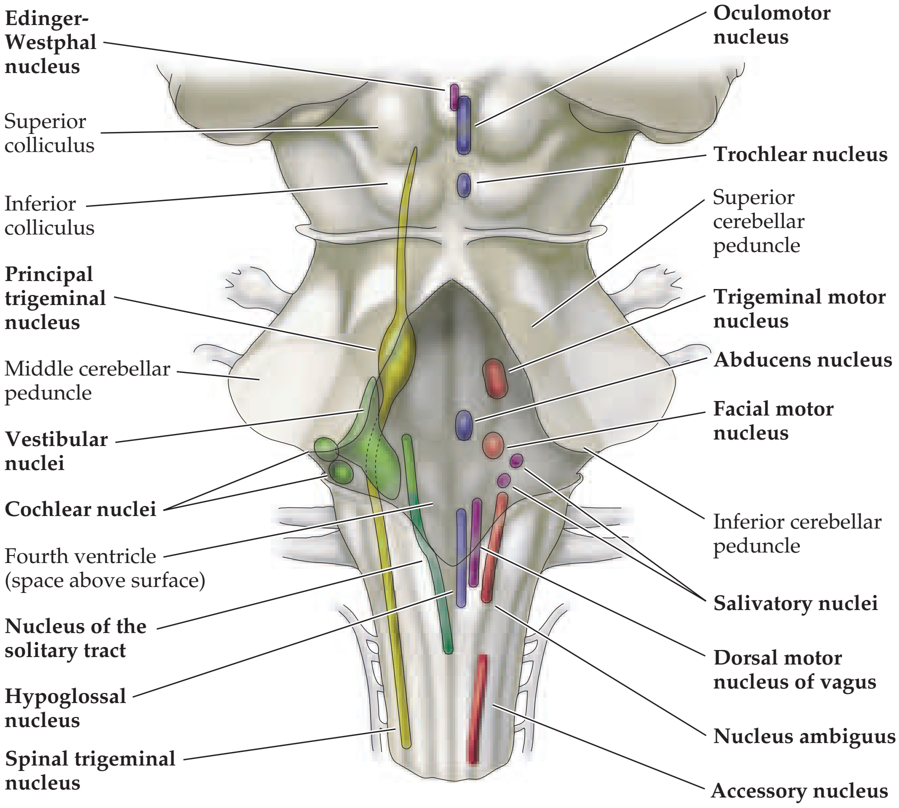

Cranial nerves
Optic chiasm
Optic tract
Mammillary body
Cerebral peduncle
Middle cerebellar peduncle
Pons
Inferior olive
Medullary pyramid
Spinal cord
Optic nerve (II)
Oculomotor nerve (III)
Trochlear nerve (IV)
Trigeminal nerve (V)
Abducens nerve (VI)
Facial nerve (VII)
Vestibulocochlear nerve (VIII)
Glossopharyngeal nerve (IX)
Vagus nerve (X)
Accessory nerve (XI)
Hypoglossal nerve (XII)
Midbrain
Pons
Medulla
Spinal cord
Color key for drawing at left:
🟨 Sensory cranial nerves
🟦 Motor cranial nerves
🟩 Mixed (sensory and motor) cranial nerves

Figure A1 At left is a ventral view of the brainstem showing the locations of the cranial nerves as they enter or exit the midbrain, pons, and medulla. Nerves that are exclusively sensory are indicated in yellow, motor nerves are in blue, and mixed sensory/motor nerves are in green. At right, the territories included in each of the brainstem subdivisions (midbrain, violet; pons, green; medulla, pink) are indicated.

TABLE A2
Classification and Location of the Cranial Nerve Nuclei[a]

Location	Somatic motor	Branchial motor	Visceral motor	General sensory	Special sensory	Visceral sensory
Midbrain	Oculomotor nucleus (III) Trochlear nucleus (IV)		Edinger-Westphal nucleus (III)	Trigeminal sensory: mesencephalic nucleus (V, VII, IX, X)		
Pons	Abducens nucleus (VI)	Trigeminal motor nucleus (V) Facial nucleus (VII)	Superior salivatory nucleus (VII) Inferior salivatory nucleus (IX)	Trigeminal sensory: principal nucleus (V, VII, IX, X)	Vestibular nuclei (VIII) Cochlear nuclei (VIII)	
Medulla	Hypoglossal nucleus (XII)	Nucleus ambiguus (IX, X) Spinal accessory nucleus (XI)	Dorsal motor nucleus of vagus (X)	Trigeminal sensory: spinal nucleus (V, VII, IX, X)		Nucleus of the solitary tract (VII, IX, X)

[a] Associated cranial nerves are shown in parentheses.


Edinger-Westphal nucleus
Superior colliculus
Inferior colliculus
Principal trigeminal nucleus
Middle cerebellar peduncle
Vestibular nuclei
Cochlear nuclei
Fourth ventricle (space above surface)
Nucleus of the solitary tract
Hypoglossal nucleus
Spinal trigeminal nucleus
Oculomotor nucleus
Trochlear nucleus
Superior cerebellar peduncle
Trigeminal motor nucleus
Abducens nucleus
Facial motor nucleus
Inferior cerebellar peduncle
Salivatory nuclei
Dorsal motor nucleus of vagus
Nucleus ambiguus
Accessory nucleus

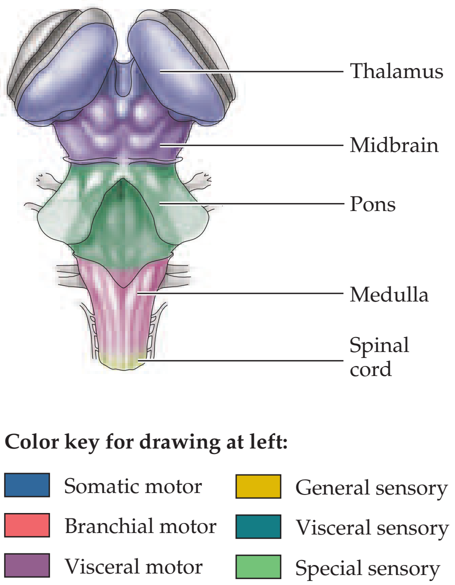
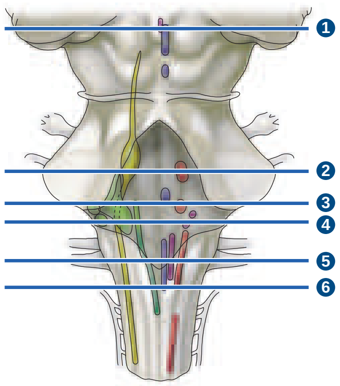

Thalamus
Midbrain
Pons
Medulla
Spinal cord
Color key for drawing at left:
🟦 Somatic motor
🟥 Branchial motor
🟪 Visceral motor
🟨 General sensory
🟦 Visceral sensory
🟩 Special sensory

Figure A2 At left, a "phantom" view of the dorsal surface of the brainstem shows the locations of the brainstem cranial nerve nuclei that are either the target or the source of the cranial nerves. (See Table A1 for the relationship between each cranial nerve and cranial nerve nuclei.) With the exception of the cranial nerve nuclei associated with the trigeminal nerve, there is fairly close correspondence between the location of the cranial nerve nuclei in the midbrain, pons, and medulla and the location of the associated cranial nerves. At right, the territories of the major brainstem subdivisions are indicated (viewed from the dorsal surface).

many enteric and visceral targets. In the pons, the sensory and motor nuclei are primarily concerned with somatic sensation from the face (the principal trigeminal nuclei); movement of the jaws and the muscles of facial expression (the trigeminal motor and facial nuclei); and abduction of the eye (the abducens nuclei). Further rostrally, in the mesencephalic portion of the brainstem, are nuclei concerned primarily with eye movements (the oculomotor and trochlear nuclei) and preganglionic parasympathetic innervation of the iris (the Edinger-Westphal nuclei). While this list is not complete, it indicates the basic order of the rostral–caudal organization of the brainstem.

Neurologists assess combinations of cranial nerve deficits to infer the location of brainstem lesions, or to place the source of brain dysfunction either in the spinal cord or brain. The most common brainstem lesions reflect the vascular territories that supply subsets of cranial nerve nuclei as well as ascending and descending tracts (see Appendix B, Figure B7). For example, an occlusion of the posterior inferior cerebellar artery (PICA), a branch of the vertebral artery that supplies the lateral region of the mid- and rostral medulla, results in damage to three cranial nerve nuclei and several tracts (see the "Upper medulla" section in Figure A3). Accordingly, there are functional deficits that reflect the loss of the spinal trigeminal nucleus, the vestibular nucleus, and the nucleus ambiguus (which contains motor neurons that project to the larynx and pharynx) on the same side as the lesion. In addition, ascending pathways from the spinal cord that relay pain and temperature from the contralateral body surface are disrupted, leading to a contralateral loss of these functions. Finally, the inferior cerebellar peduncle, which contains projections that relay information about body position to the cerebellum for postural control, is damaged. This loss results in ataxia (clumsiness) on

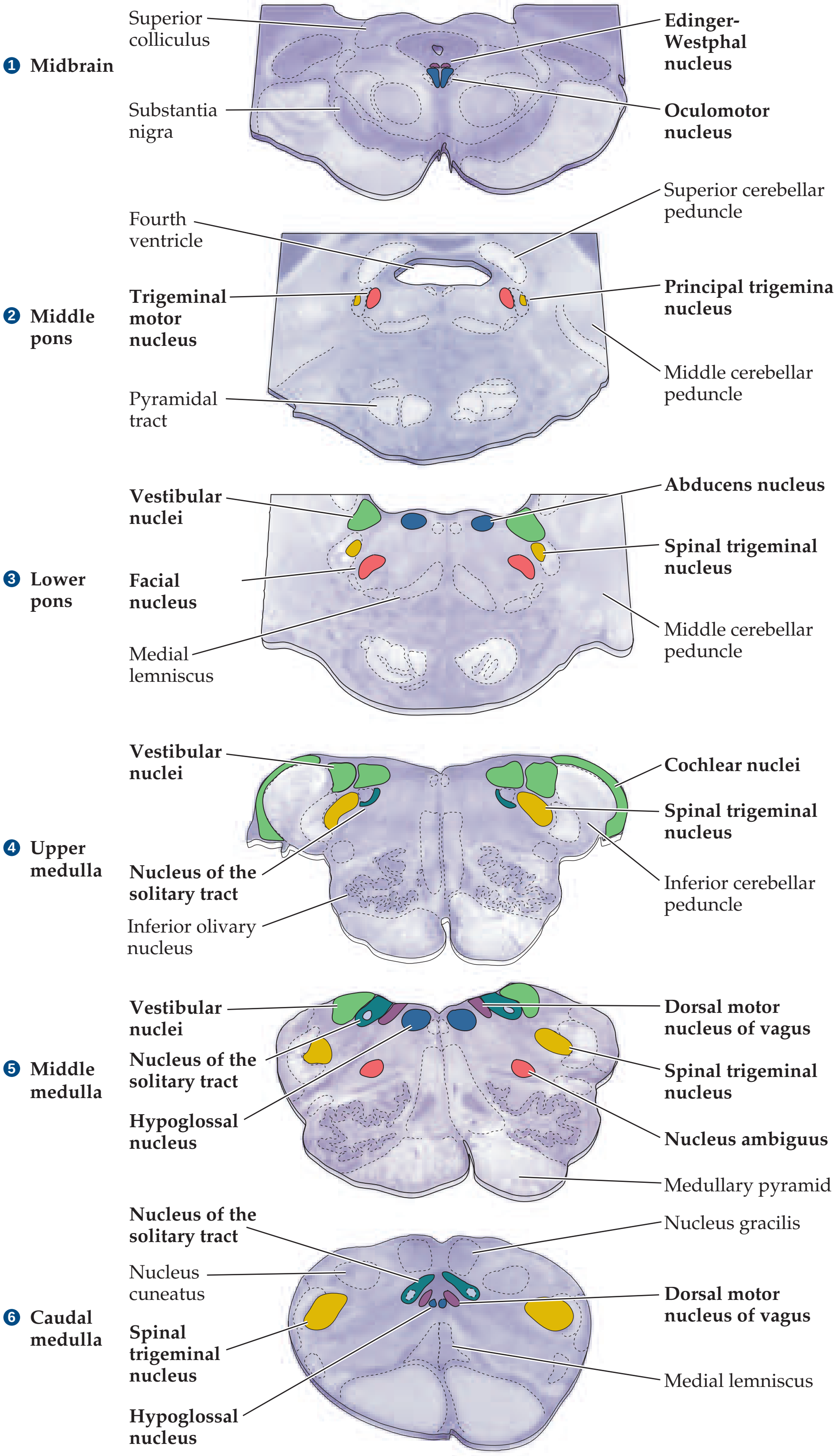


Color key for cranial nerve nuclei:

- 🟦 Somatic motor
- 🟥 Branchial motor
- 🟪 Visceral motor

- 🟨 General sensory
- ■ Visceral sensory
- 🟩 Special sensory

Figure A3 Transverse sections through the brainstem and spinal cord showing internal organization along the rostral–caudal axis. The locations of the cranial nerve nuclei, ascending, and descending tracts are indicated in each representative section. The identity of the nuclei (somatic sensory or motor; visceral sensory or motor; branchial sensory or motor) is indicated using the same color key as in Figure A2. The vascular territories for these brainstem sections are illustrated in Appendix B, Figure B7.


❶ Midbrain
Superior colliculus
Substantia nigra
Edinger-Westphal nucleus
Oculomotor nucleus
❷ Middle pons
Fourth ventricle
Trigeminal motor nucleus
Pyramidal tract
Superior cerebellar peduncle
Principal trigeminal nucleus
Middle cerebellar peduncle
❸ Lower pons
Vestibular nuclei
Facial nucleus
Medial lemniscus
Abducens nucleus
Spinal trigeminal nucleus
Middle cerebellar peduncle
❹ Upper medulla
Vestibular nuclei
Nucleus of the solitary tract
Inferior olivary nucleus
Cochlear nuclei
Spinal trigeminal nucleus
Inferior cerebellar peduncle
❺ Middle medulla
Vestibular nuclei
Nucleus of the solitary tract
Hypoglossal nucleus
Dorsal motor nucleus of vagus
Spinal trigeminal nucleus
Nucleus ambiguus
Medullary pyramid
❻ Caudal medulla
Nucleus of the solitary tract
Nucleus cuneatus
Spinal trigeminal nucleus
Hypoglossal nucleus
Nucleus gracilis
Dorsal motor nucleus of vagus
Medial lemniscus

the side of the lesion. Anatomical relationships and shared vascularization, rather than any functional principle, unite these deficits and allow clinical localization of brainstem damage. For both clinicians and neurobiologists, understanding the brainstem requires integrating anatomical information with knowledge about functional organization and pathology.

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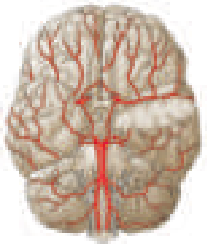
Appendix B



Vascular Supply, the Meninges, and the Ventricular System

The Blood Supply of the Brain and Spinal Cord

Understanding the blood supply of the brain and spinal cord is crucial for the practice of medicine, particularly for neurology and neurosurgery. Damage to major blood vessels by trauma or stroke results in combinations of functional defects reflecting local cell death as well as the disruption of axons passing through the region compromised by the vascular damage. Thus, a firm knowledge of the major cerebral blood vessels and the neuroanatomical territories they perfuse facilitates the initial diagnoses of a broad range of brain damage and disease.

The entire blood supply of the brain and spinal cord depends on two sets of branches from the dorsal aorta. The **vertebral arteries** arise from the subclavian arteries, and the **internal carotid arteries** are branches of the common carotid arteries. The vertebral arteries and the ten **medullary arteries** that arise from segmental branches of the aorta provide the primary vascularization of the spinal cord. These medullary arteries join to form the **anterior** and **posterior spinal arteries** (Figure B1). If any of the medullary arteries are obstructed or damaged (during abdominal surgery, for example), the blood supply to specific parts of the spinal cord may be compromised. The pattern of resulting neurological damage differs according to whether supply to the posterior or anterior artery is interrupted. As might be expected from the arrangement of ascending and descending neural pathways in the spinal cord, loss of the posterior supply generally leads to loss of sensory functions, whereas loss of the anterior supply more often causes motor deficits.

Anterior to the spinal cord and brainstem, the **internal carotid arteries** branch to form two major cerebral arteries, the **anterior** and **middle cerebral arteries**. The right and left **vertebral arteries** come together at the level of the pons on the ventral surface of the brainstem to form the midline **basilar artery**. The basilar artery joins the blood supply from the internal carotids in an arterial ring at the base of the brain (in the vicinity of the hypothalamus and cerebral peduncles) called the **circle of Willis**. The **posterior cerebral arteries** arise at this confluence, as do two small bridging arteries, the **anterior** and **posterior communicating arteries**. Conjoining the two major sources of cerebral vascular supply via the circle of Willis presumably improves the chances of any region of the brain continuing to receive blood if one of the major arteries becomes occluded (see Box A).

The major branches that arise from the internal carotid artery—the anterior and middle cerebral arteries—form the **anterior circulation** that supplies the forebrain (Figure B2). These arteries branch from the internal carotids within the circle of Willis. Each gives rise to branches that supply the cortex and branches that penetrate the basal surface of the brain, supplying deep

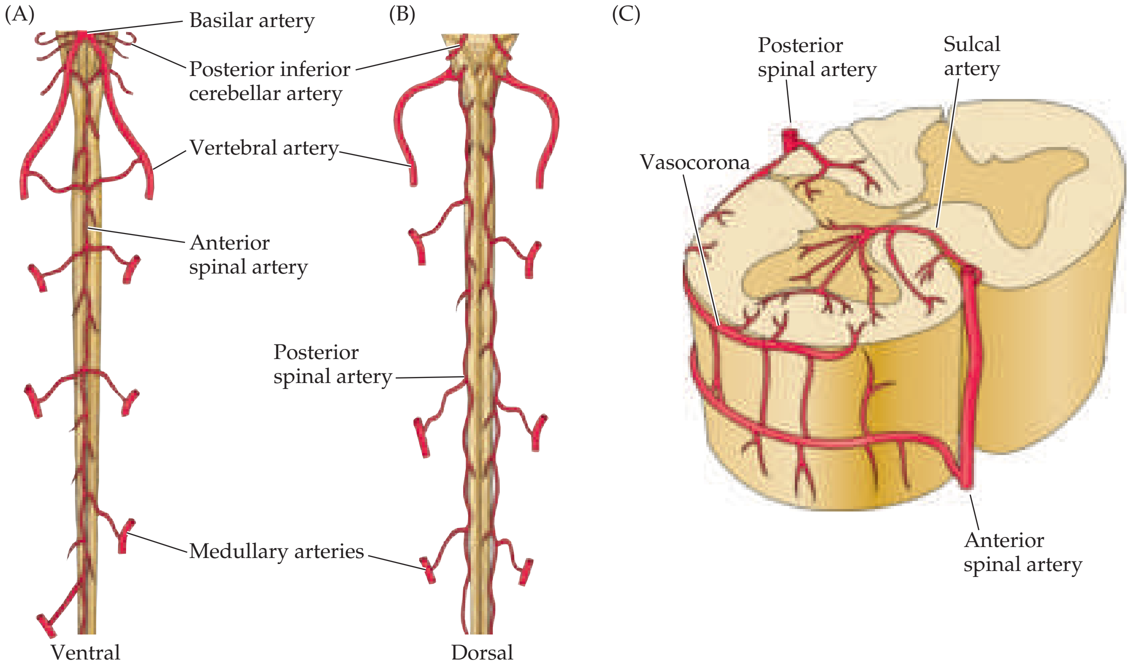


Figure B1 Blood supply of the spinal cord. (A) View of the ventral (anterior) surface of the spinal cord. At the level of the medulla, the vertebral arteries give off branches that merge to form the anterior spinal artery. Approximately 10 to 12 segmental arteries (which arise from various branches of the aorta) join the anterior spinal artery along its course. These segmental arteries are known as medullary arteries. (B) The vertebral arteries (or the posterior inferior cerebellar artery) give rise to paired posterior spinal arteries that run along the dorsal (posterior) surface of the spinal cord. (C) Cross section through the spinal cord, illustrating the distribution of the anterior and posterior spinal arteries. The anterior spinal arteries give rise to numerous sulcal branches that supply the anterior two-thirds of the spinal cord. The posterior spinal arteries supply much of the dorsal horn and the dorsal columns. A network of vessels known as the vasocorona connects these two sources of supply and sends branches into the white matter around the margin of the spinal cord.

structures such as the basal ganglia, thalamus, and internal capsule. Particularly prominent are the **lenticulostriate arteries** that branch from the middle cerebral artery. These arteries supply the basal ganglia and thalamus. The **posterior circulation** of the brain supplies the posterior cerebral cortex, the midbrain, and the brainstem; it comprises arterial branches arising from the **posterior cerebral**, **basilar**, and **vertebral arteries**. The pattern of arterial distribution is similar for all the subdivisions of the brainstem: midline arteries supply medial structures, lateral arteries supply the lateral brainstem, and dorsal-lateral arteries supply dorsal-lateral brainstem structures and the cerebellum (Figures B2 and B3). Among the most important dorsal-lateral arteries (also called **long circumferential** arteries) are the **posterior inferior cerebellar artery** (**PICA**) and the **anterior inferior cerebellar artery** (**AICA**), which supply distinct regions of the medulla and pons. These arteries, as well as branches of the basilar artery that penetrate the brainstem from its ventral and lateral surfaces (called **paramedian** and **short circumferential** arteries), are especially common sites of occlusion and result in specific functional deficits of cranial nerve, somatic sensory, and motor function (see Appendix A).

The physiological demands served by the blood supply of the brain are particularly significant because neurons are more sensitive to oxygen deprivation than other kinds of cells with lower rates of metabolism. In addition, the brain is at risk from circulating toxins, and is specifically protected in this respect by the **blood-brain barrier** (see below). As a result of the high metabolic rate of neurons, brain tissue deprived of oxygen and glucose as a result of compromised blood supply is likely to sustain transient or permanent damage. Brief loss of blood supply (referred to as ischemia) can cause cellular changes, which, if not quickly reversed, can lead to cell death. Sustained loss of blood supply leads much more directly to death and degeneration of the deprived cells. Strokes—an anachronistic term that refers to the death or dysfunction of brain tissue due to vascular disease—often follow the occlu-

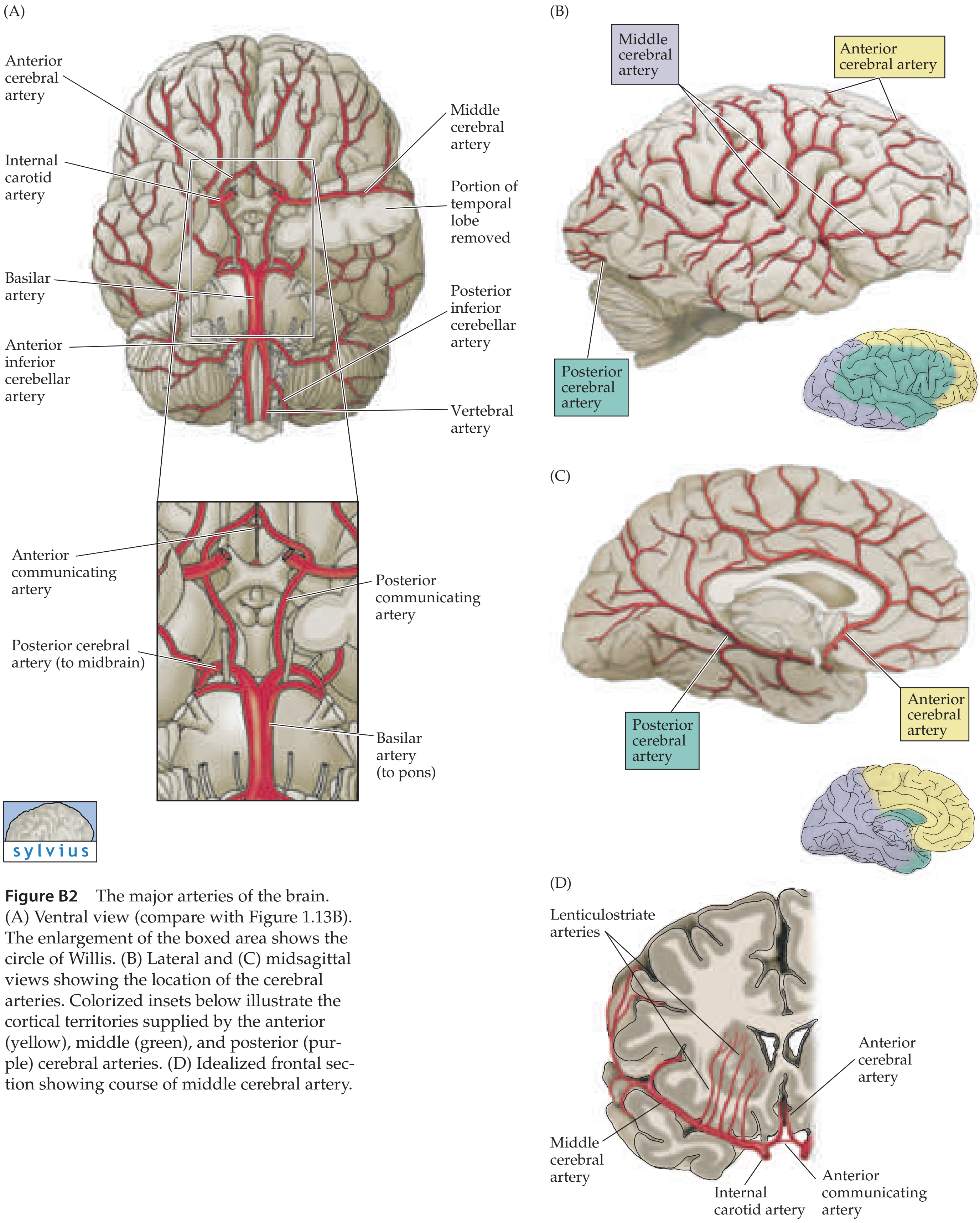

(A)
Anterior cerebral artery
Internal carotid artery
Basilar artery
Anterior inferior cerebellar artery
Middle cerebral artery
Portion of temporal lobe removed
Posterior inferior cerebellar artery
Vertebral artery
Anterior communicating artery
Posterior cerebral artery (to midbrain)
Posterior communicating artery
Basilar artery (to pons)
sylvius
(B)
Middle cerebral artery
Anterior cerebral artery
Posterior cerebral artery
(C)
Posterior cerebral artery
Anterior cerebral artery
(D)
Lenticulostriate arteries
Anterior cerebral artery
Middle cerebral artery
Internal carotid artery
Anterior communicating artery

Figure B2 The major arteries of the brain. (A) Ventral view (compare with Figure 1.13B). The enlargement of the boxed area shows the circle of Willis. (B) Lateral and (C) midsagittal views showing the location of the cerebral arteries. Colorized insets below illustrate the cortical territories supplied by the anterior (yellow), middle (green), and posterior (purple) cerebral arteries. (D) Idealized frontal section showing course of middle cerebral artery.

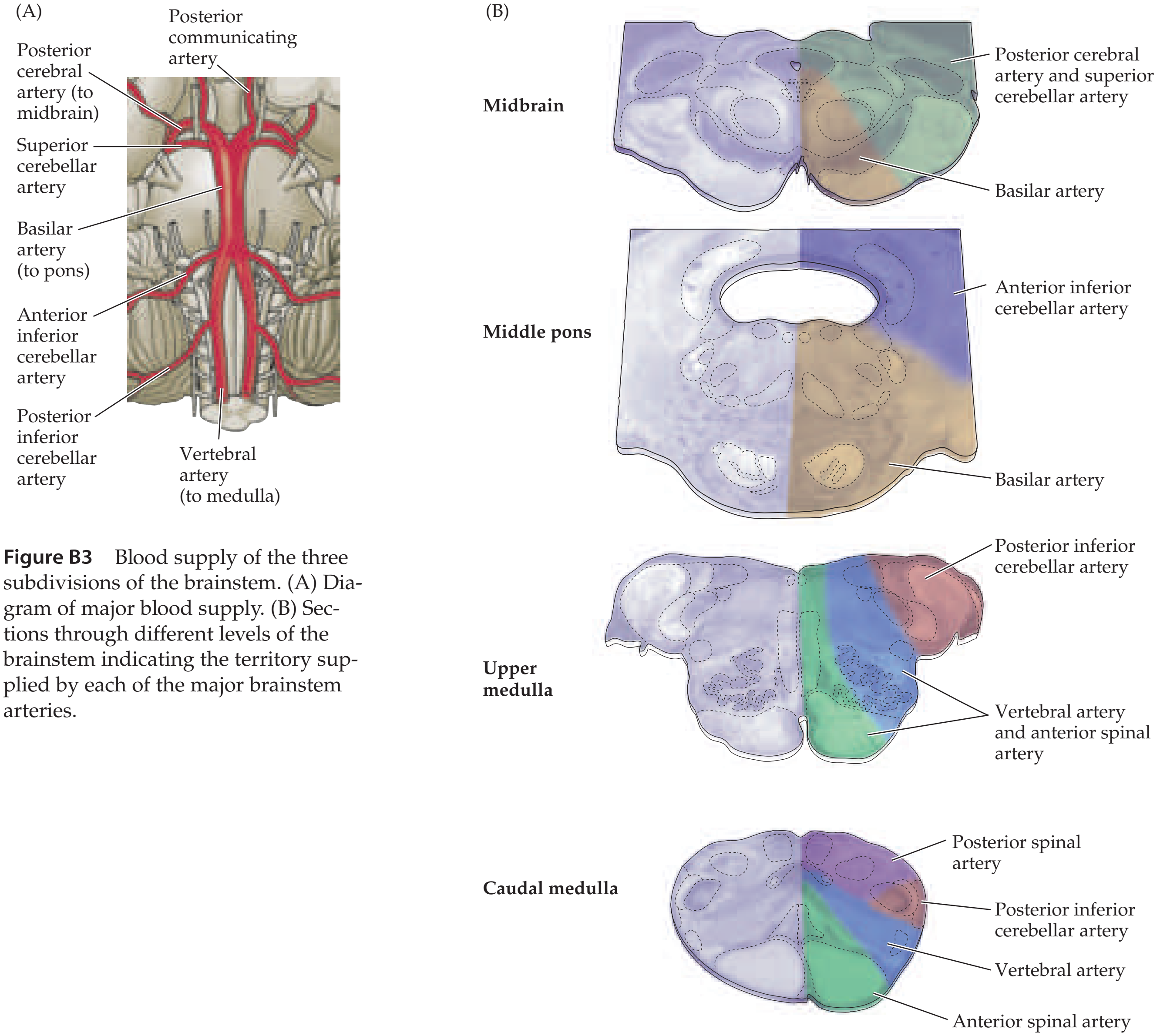

(A)
Posterior communicating artery
Posterior cerebral artery (to midbrain)
Superior cerebellar artery
Basilar artery (to pons)
Anterior inferior cerebellar artery
Posterior inferior cerebellar artery
Vertebral artery (to medulla)
(B)
Midbrain
Posterior cerebral artery and superior cerebellar artery
Basilar artery
Middle pons
Anterior inferior cerebellar artery
Basilar artery
Upper medulla
Posterior inferior cerebellar artery
Vertebral artery and anterior spinal artery
Caudal medulla
Posterior spinal artery
Posterior inferior cerebellar artery
Vertebral artery
Anterior spinal artery

Figure B3 Blood supply of the three subdivisions of the brainstem. (A) Diagram of major blood supply. (B) Sections through different levels of the brainstem indicating the territory supplied by each of the major brainstem arteries.

sion of (or hemorrhage from) the brain's arteries (Box A). Historically, studies of the functional consequences of strokes, and their relation to vascular territories in the brain and spinal cord, provided information about the location of various brain functions. The location of the major language functions in the left hemisphere, for instance, was discovered in this way in the latter part of the nineteenth century (see Chapter 26). Now, noninvasive functional imaging techniques based on blood flow (see Box A In Chapter 1) have largely supplanted the correlation of clinical signs and symptoms with the location of tissue damage observed at autopsy.

The Blood-Brain Barrier

The interface between the walls of capillaries and the surrounding tissue is important throughout the body, as it keeps vascular and extravascular concen-

Box A
Stroke

Stroke is the most common neurological cause for admission to a hospital, and is the third leading cause of death in the United States (after heart disease and cancer). The term "stroke" refers to the sudden appearance of a limited neurological deficit, such as weakness or paralysis of a limb, or the sudden inability to speak. The onset of the deficit within seconds, minutes, or hours marks the problem a vascular one. Brain function is exquisitely dependent on a continuous supply of oxygen, as evidenced by the onset of unconsciousness within about 10 seconds of blocking its blood supply (by cardiac arrest, for instance). The damage to neurons is at first reversible, but eventually becomes permanent if the blood supply is not promptly restored.

Strokes can be subdivided into three main types: thrombotic, embolic, and hemorrhagic. The thrombotic variety is caused by a local reduction of blood flow arising from an atherosclerotic buildup in one of the cerebral blood vessels that eventually occludes it. Alternatively, a reduction of blood flow can arise when an embolus (meaning an object loose in the bloodstream) dislodges from the heart (or from an atherosclerotic plaque in the carotid or vertebral arteries) and travels to a cerebral artery (or arteriole) where it forms a plug. A hemorrhagic stroke occurs when a cerebral blood vessel ruptures, as can occur as a result of hypertension, a congenital aneurysm (bulging of a vessel), or a congenital arterio-venous malformation. The relative frequency of thrombotic, embolic, and hemorrhagic strokes is approximately 50%, 30%, and 20%, respectively.

The diagnosis of stroke relies primarily on an accurate history and a competent neurological examination. Indeed, the neurologist C. Miller Fisher, a master of bedside diagnosis, remarked that medical students and residents should learn neurology "stroke by stroke." Understanding the portion of the brain supplied by each of the major arteries (see text) enables an astute clinician to identify the occluded blood vessel.

More recently, imaging techniques such as CT scans and MRI (see Box A in Chapter 1) have greatly facilitated the physician's ability to identify and localize small hemorrhages and regions of permanently damaged tissue. Moreover, Doppler ultrasound, magnetic resonance angiography, and imaging of blood vessels by direct infusion of radio-opaque dye can now pinpoint atherosclerotic plaques, aneurysms, and other vascular abnormalities.

Several therapeutic approaches to strokes are feasible. Dissolving a thrombotic plug by tissue plasminogen activator (TPA) and other compounds is now standard clinical practice for selected stroke victims. Furthermore, recent understanding of some of the mechanisms by which ischemia injures brain tissue has made pharmacological strategies to minimize neuronal injury after stroke a potentially effective possibility (see Box D in Chapter 6). Hemorrhagic strokes are treated neurosurgically by finding and stopping the bleeding from the defective vessel (when that is technically possible).

These approaches can minimize functional loss; however, strokes remain a serious health risk from which there is never full recovery. The inability of the mature brain to replace large populations of damaged or dead neurons, or to repair long axon tracts once they have been compromised, invariably prevents the complete restoration of lost functions.

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Adams, R. D., M. Victor and A. H. Ropper (2001) *Principles of Neurology*, 7th Ed. New York: McGraw-Hill, Ch. 34, pp. 821–924.

trations of ions and molecules at appropriate levels in these two compartments. In the brain, this interface is especially significant and has been accorded an alliterative name, "the blood-brain barrier." The special properties of the blood-brain barrier were first observed by the nineteenth-century bacteriologist Paul Ehrlich, who noted that intravenously injected dyes leaked out of capillaries in most regions of the body to stain the surrounding tissues; the brain, however, remained unstained. Ehrlich wrongly concluded that the brain had a low affinity for the dyes; his student, Edwin Goldmann, showed that such dyes do not traverse the specialized walls of brain capillaries.

The restriction of large molecules like Ehrlich's dyes (and many smaller molecules) to the vascular space is the result of tight junctions between neighboring capillary endothelial cells in the brain (Figure B4). Such junctions are not found in capillaries elsewhere in the body, where the spaces between adjacent endothelial cells allow much more ionic and molecular

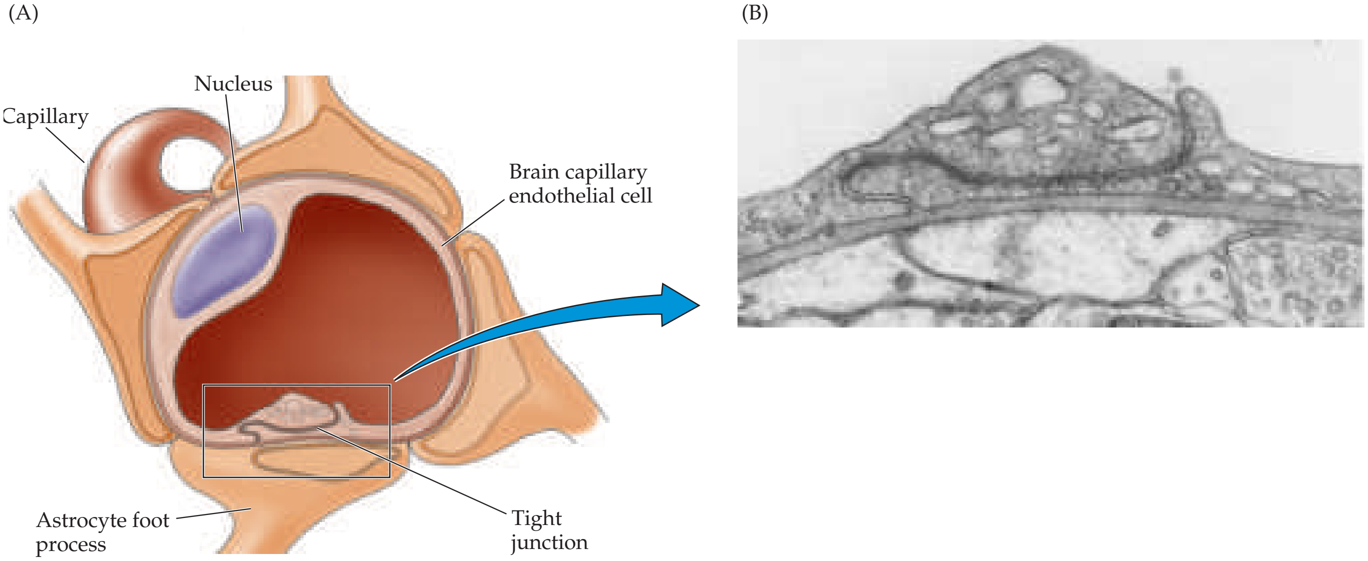


Figure B4 The cellular basis of the blood-brain barrier. (A) Diagram of a brain capillary in cross section and reconstructed views, showing endothelial tight junctions and the investment of the capillary by astrocytic end feet. (B) Electron micrograph of boxed area in (A), showing the appearance of tight junctions between neighboring endothelial cells (arrows). (A after Goldstein and Betz, 1986; B from Peters et al., 1991.)

traffic. The structure of tight junctions was first demonstrated in the 1960s by Tom Reese, Morris Karnovsky, and Milton Brightman. Using electron microscopy after the injection of electron-dense intravascular agents such as lanthanum salts, they showed that the close apposition of the endothelial cell membranes prevented such ions from passing (panel B in Figure B4). Substances that traverse the walls of brain capillaries must move *through* the endothelial cell membranes. Accordingly, molecular entry into the brain should be determined by an agent's solubility in lipids, the major constituent of cell membranes. Nevertheless, many ions and molecules not readily soluble in lipids *do* move quite readily from the vascular space into brain tissue. A molecule like glucose, the primary source of metabolic energy for neurons and glial cells, is an obvious example. This paradox is explained by the presence of specific transporters for glucose and other critical molecules and ions.

In addition to tight junctions, astrocytic "end feet" (the terminal regions of astrocytic processes) surround the outside of capillary endothelial cells. The reason for this endothelial–glial allegiance is unclear, but may reflect an influence of astrocytes on the formation and maintenance of the blood-brain barrier.

The brain, more than any other organ, must be carefully shielded from abnormal variations in its ionic milieu, as well as from the potentially toxic molecules that find their way into the vascular space by ingestion, infection, or other means. The blood-brain barrier is thus important for protection and homeostasis. It also presents a significant problem for the delivery of drugs to the brain. Large (or lipid-insoluble) molecules can be introduced to the brain, but only by transiently disrupting the blood-brain barrier with hyperosmotic agents like mannitol.

The Meninges

The cranial cavity is conventionally divided into three regions called the anterior, middle, and posterior cranial fossae. Surrounding and supporting the brain within this cavity are three protective tissue layers, which also extend down the brainstem and the spinal cord. Together these layers are

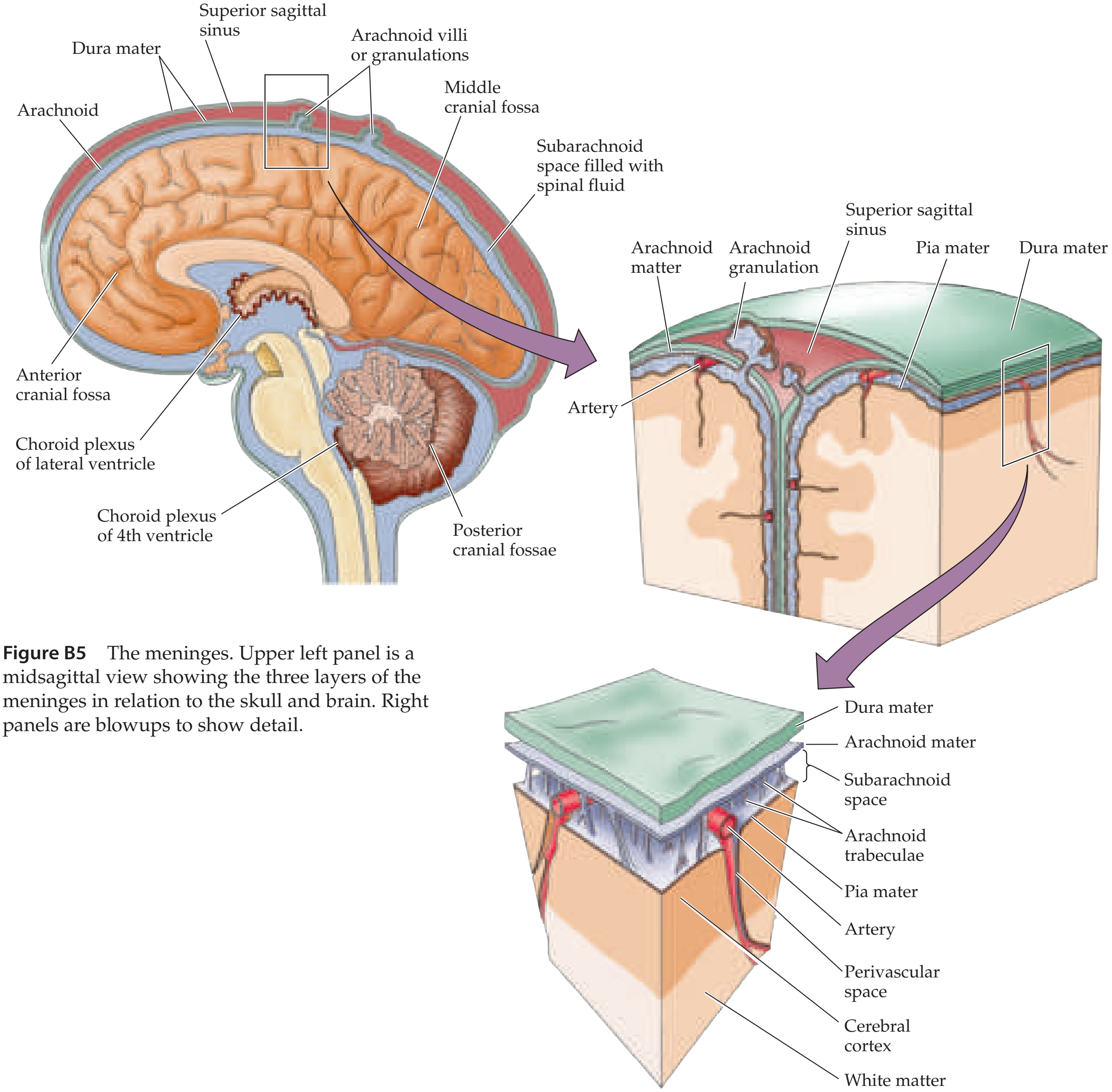

Superior sagittal sinus
Dura mater
Arachnoid villi or granulations
Arachnoid
Middle cranial fossa
Subarachnoid space filled with spinal fluid
Anterior cranial fossa
Choroid plexus of lateral ventricle
Choroid plexus of 4th ventricle
Posterior cranial fossae
Superior sagittal sinus
Arachnoid matter
Arachnoid granulation
Pia mater
Dura mater
Artery
Dura mater
Arachnoid mater
Subarachnoid space
Arachnoid trabeculae
Pia mater
Artery
Perivascular space
Cerebral cortex
White matter

Figure B5 The meninges. Upper left panel is a midsagittal view showing the three layers of the meninges in relation to the skull and brain. Right panels are blowups to show detail.

called the **meninges** (Figure B5). The outermost layer of the meninges is called the **dura mater** (meaning "hard mother," because it is thick and tough). The middle layer is called the **arachnoid mater** because of spiderlike processes called arachnoid trabiculae that extend from it toward the third layer, the **pia mater**, a thin, delicate layer of cells that closely invests the surface of the brain. Since the pia closely adheres to the brain as its surface curves and folds, whereas the arachnoid does not, there are places—called **cisterns**—where the subarachnoid space enlarges to form significant collections of CSF. The major arteries supplying the brain course through the subarachnoid space where they give rise to branches that penetrate the substance of the hemispheres. The subarachnoid space is therefore a frequent site of bleeding following trauma. A collection of blood between the meningeal layers is referred to as a subdural or subarachnoid hemorrhage, as distinct from bleeding within the brain itself.

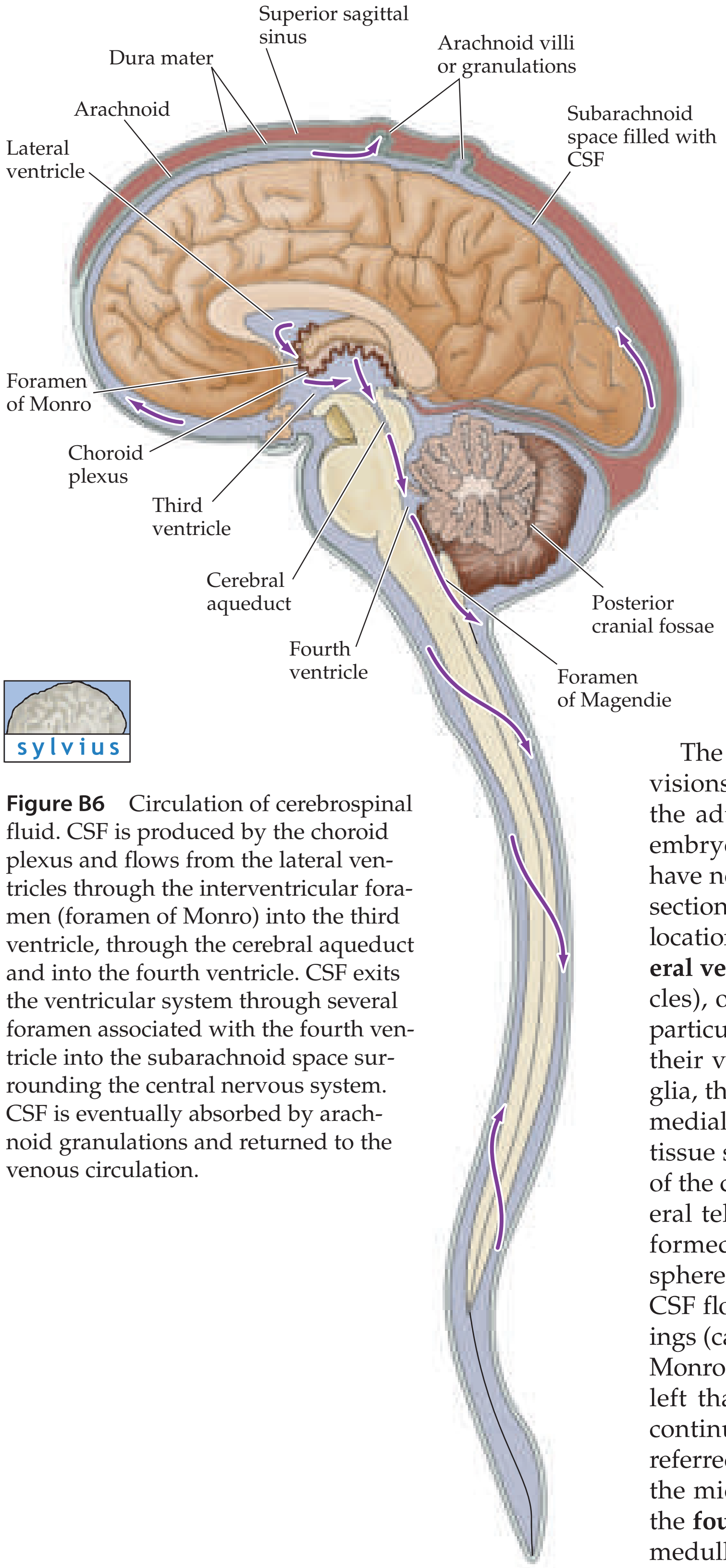


Figure B6 Circulation of cerebrospinal fluid. CSF is produced by the choroid plexus and flows from the lateral ventricles through the interventricular foramen (foramen of Monro) into the third ventricle, through the cerebral aqueduct and into the fourth ventricle. CSF exits the ventricular system through several foramen associated with the fourth ventricle into the subarachnoid space surrounding the central nervous system. CSF is eventually absorbed by arachnoid granulations and returned to the venous circulation.

The Ventricular System

The cerebral ventricles are a series of interconnected, fluid-filled spaces that lie in the core of the forebrain and brainstem (Figures B6 and B7). These spaces are filled with **cerebrospinal fluid (CSF)** that is produced by a modified vascular structure referred to as the **choroid plexus,** which is present in each of the ventricles. The cerebrospinal fluid percolates through the ventricular system and flows into the subarachnoid space through perforations in the thin covering of the fourth ventricle (see Figure B6); it is eventually absorbed by specialized structures called arachnoid villi or granulations (see Figure B5), and returned to the venous circulation.

The presence of ventricular spaces in the various subdivisions of the brain reflects the fact that the ventricles are the adult derivatives of the open space or lumen of the embryonic neural tube (see Chapter 21). Although they have no unique function, the ventricular spaces present in sections through the brain provide another useful guide to location (Figure B8). The largest of these spaces are the **lateral ventricles (**formerly called the first and second ventricles), one within each of the cerebral hemispheres. These particular ventricles are best seen in frontal sections, where their ventral surface is usually defined by the basal ganglia, their dorsal surface by the corpus callosum, and their medial surface by the **septum pellucidum**, a membranous tissue sheet that forms part of the midline sagittal surface of the cerebral hemispheres. The lateral ventricles, like several telencephalic structures, possess a "C" shape that is formed by the non-uniform growth of the cerebral hemispheres during embryonic development (see Figure 21.5). CSF flows from the lateral ventricles through small openings (called the interventricular foramen, or the foramen of Monro) into a narrow midline space between the right and left thalamus, the **third ventricle.** The third ventricle is continuous caudally with the **cerebral aqueduct** (also referred to as the aqueduct of Sylvius), which runs though the midbrain. At its caudal end, the aqueduct opens into the **fourth ventricle**, a larger space in the dorsal pons and medulla. The fourth ventricle, covered on its dorsal aspect by the cerebellum, narrows caudally to form the central canal of the spinal cord.

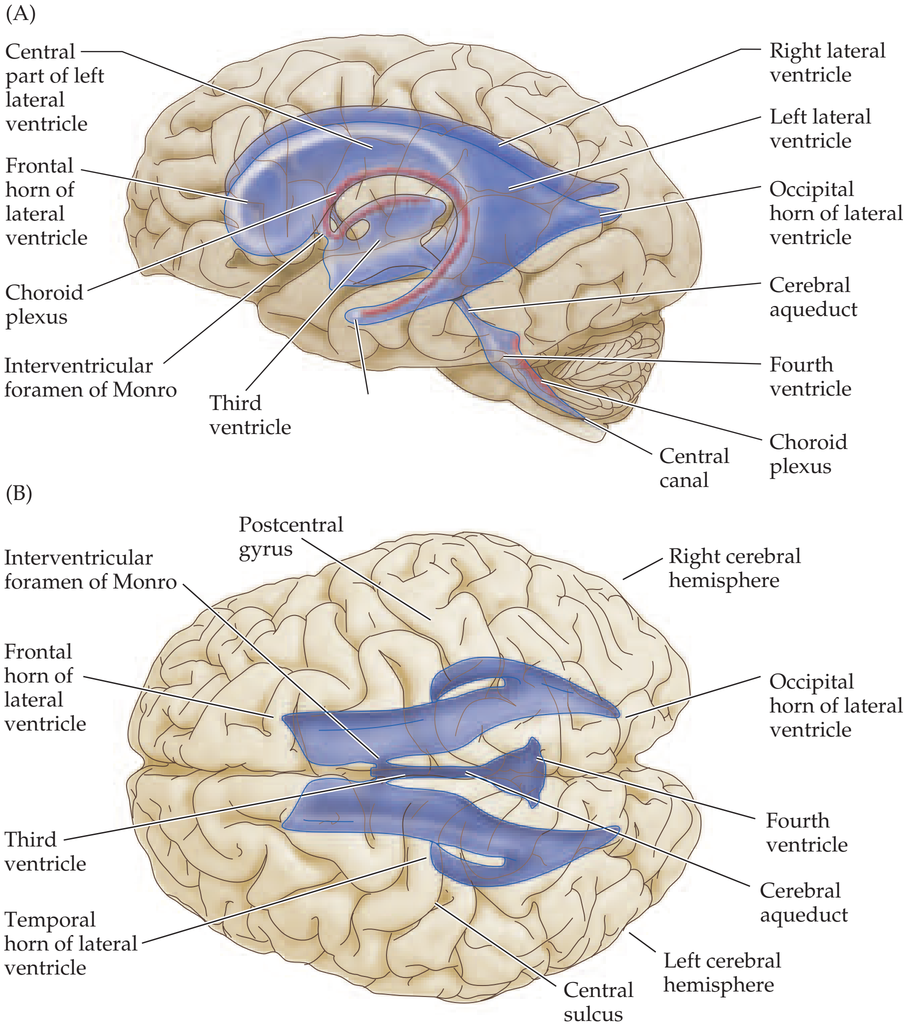
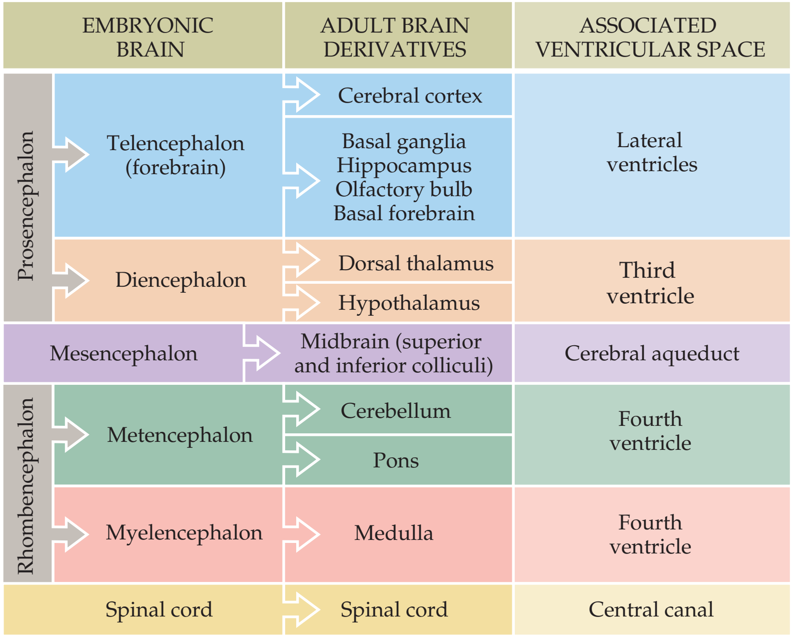

(A)
Central part of left lateral ventricle
Frontal horn of lateral ventricle
Choroid plexus
Interventricular foramen of Monro
Third ventricle
Right lateral ventricle
Left lateral ventricle
Occipital horn of lateral ventricle
Cerebral aqueduct
Fourth ventricle
Choroid plexus
Central canal
(B)
Interventricular foramen of Monro
Postcentral gyrus
Right cerebral hemisphere
Frontal horn of lateral ventricle
Occipital horn of lateral ventricle
Fourth ventricle
Third ventricle
Cerebral aqueduct
Temporal horn of lateral ventricle
Left cerebral hemisphere
Central sulcus

Figure B7 The ventricular system of the human brain. (A) Location of the ventricles as seen in a transparent left lateral view. (B) Dorsal view of the ventricles. (C) Table showing the ventricular spaces associated with each of the major subdivisions of the brain. (See Chapter 21 for an account of brain development that more fully explains the origin of the ventricular spaces.)

(C)



EMBRYONIC BRAIN		ADULT BRAIN DERIVATIVES	ASSOCIATED VENTRICULAR SPACE
Prosencephalon	Telencephalon (forebrain)	Cerebral cortex	Lateral ventricles
		Basal ganglia Hippocampus Olfactory bulb Basal forebrain	
	Diencephalon	Dorsal thalamus	Third ventricle
		Hypothalamus	
Mesencephalon		Midbrain (superior and inferior colliculi)	Cerebral aqueduct
Rhombencephalon	Metencephalon	Cerebellum	Fourth ventricle
		Pons	
	Myelencephalon	Medulla	Fourth ventricle
Spinal cord		Spinal cord	Central canal

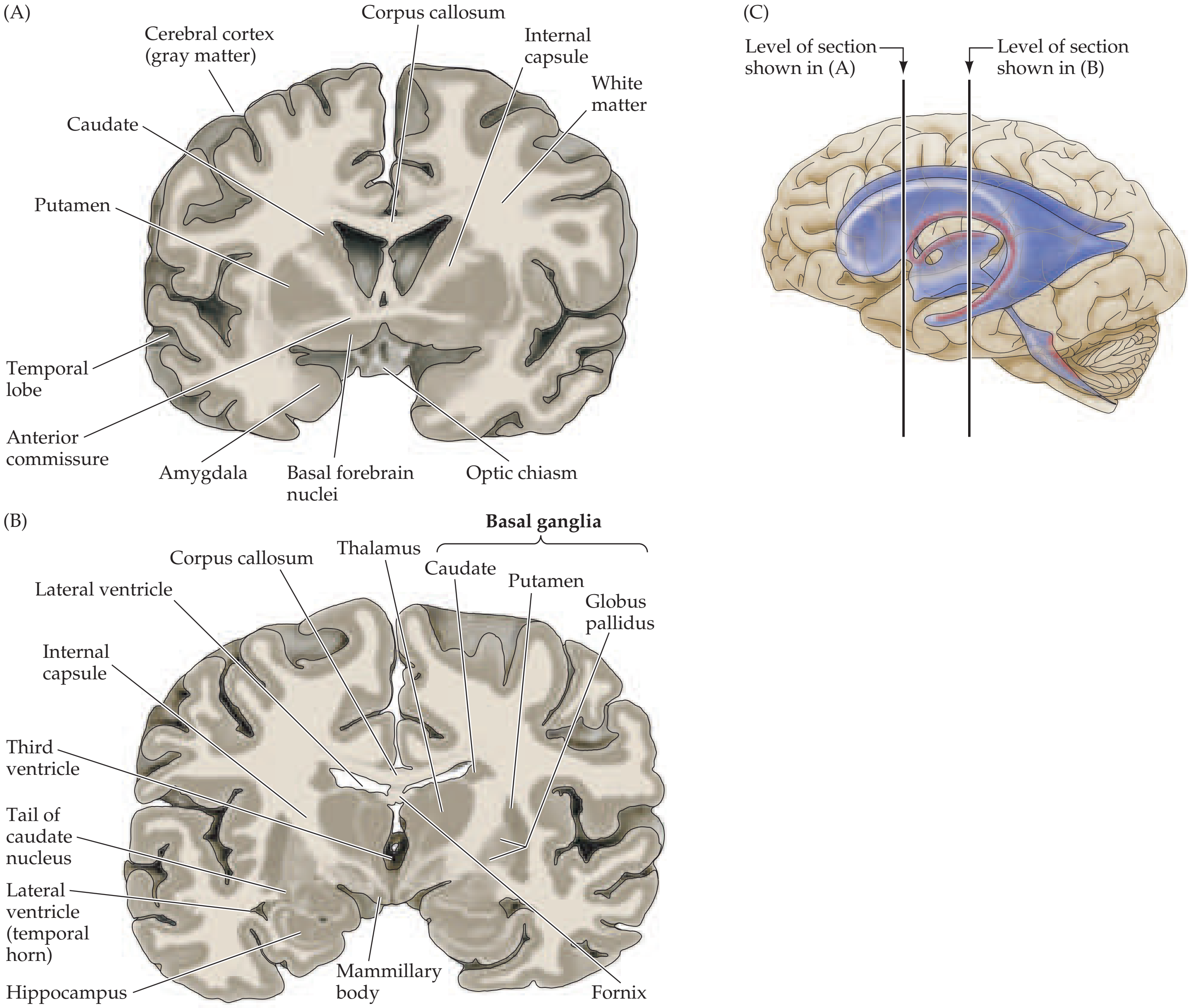

(A)
Corpus callosum
Cerebral cortex (gray matter)
Internal capsule
White matter
Caudate
Putamen
Temporal lobe
Anterior commissure
Amygdala
Basal forebrain nuclei
Optic chiasm
(C)
Level of section shown in (A)
Level of section shown in (B)
(B)
Basal ganglia
Corpus callosum
Thalamus
Caudate
Putamen
Globus pallidus
Lateral ventricle
Internal capsule
Third ventricle
Tail of caudate nucleus
Lateral ventricle (temporal horn)
Hippocampus
Mammillary body
Fornix

Figure B8 The ventricular system as seen in coronal brain sections. (A, B) Location the ventricles in coronal section. Notice that the lateral ventricle appears twice in section (B). (C) A transparent view of the ventricular system indicating the approximate location of the sections in (A) and (B).

The normal total volume of CSF in the ventricular system is approximately 140 mL. The choroid plexus produces approximately 500 mL of CSF per day, so that the entire volume present in the system is turned over several times a day. Thus, impaired absorption or obstruction of CSF flow results in an excess of cerebrospinal fluid in the intracranial cavity, a condition called **hydrocephalus** (literally, “water head”).

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Glossary

acetylcholine Neurotransmitter at motor neuron synapses, in autonomic ganglia and a variety of central synapses; binds to two types of receptors: ligand-gated ion channels (nicotinic receptors) and G-protein-coupled receptors (muscarinic receptors).

achromatopsia, cerebral Loss of color vision as a result of damage to extrastriate visual cortex.

action potential The electrical signal conducted along axons (or muscle fibers) by which information is conveyed from one place to another in the nervous system.

activation The time-dependent opening of ion channels in response to a stimulus, typically membrane depolarization.

adaptation The phenomenon of sensory receptor adjustment to different levels of stimulation; critical for allowing sensory systems to operate over a wide dynamic range.

adenylyl cyclase Membrane-bound enzyme that can be activated by G-proteins to catalyze the synthesis of cyclic AMP from ATP.

adhesion molecules see cell adhesion molecules.

adrenaline see epinephrine.

adrenal medulla The central part of the adrenal gland that, under visceral motor stimulation, secretes epinephrine and norepinephrine into the bloodstream.

adrenergic Refers to synaptic transmission mediated by the release of norepinephrine or epinephrine.

adult The mature form of an animal, usually defined by the ability to reproduce.

afferent An axon that conducts action potentials from the periphery toward the central nervous system.

agnosia The inability to name objects.

alpha (α) motor neurons Neurons in the ventral horn of the spinal cord that innervate skeletal muscle.

amacrine cells Retinal neurons that mediate lateral interactions between bipolar cell terminals and the dendrites of ganglion cells.

amblyopia Diminished visual acuity as a result of the failure to establish appropriate visual cortical connections in early life.

amnesia The pathological inability to remember or establish memories; retrograde amnesia is the inability to recall existing memories, whereas anterograde amnesia is the inability to lay down new memories.

amphetamine A synthetically produced central nervous system stimulant with cocaine-like effects; drug abuse may lead to dependence.

ampullae The juglike swellings at the base of the semicircular canals that contain the hair cells and cupulae (see also cupulae).

amygdala A nuclear complex in the temporal lobe that forms part of the limbic system; its major functions concern autonomic, emotional, and sexual behavior.

androgen insensitivity syndrome A condition in which, due to a defect in the gene that codes for the androgen receptor, testosterone cannot act on its target tissues.

anencephaly A congenital defect of neural tube closure, in which much of the brain fails to develop.

anosmia Loss of the sense of smell.

anterior Toward the front; sometimes used as a synonym for rostral, and sometimes as a synonym for ventral.

anterior commissure A small midline fiber tract that lies at the anterior end of the corpus callosum; like the callosum, it serves to connect the two hemispheres.

anterior hypothalamus Region of the hypothalamus containing nuclei that mediate sexual behaviors; not to be confused with region in rodent called the medial preoptic area, which lies anterior to hypothalamus and also contains nuclei that mediate sexual behavior (most notably the sexually dimorphic nucleus).

anterograde A movement or influence acting from the neuronal cell body toward the axonal target.

anterolateral pathway (anterolateral system) Ascending sensory pathway in the spinal cord and brainstem that carries information about pain and temperature to the thalamus.

antiserum Serum harvested from an animal immunized to an agent of interest.

aphasia The inability to comprehend and/or produce language as a result of damage to the language areas of the cerebral cortex (or their white matter interconnections).

apoptosis Cell death resulting from a programmed pattern of gene expression; also known as "programmed cell death."

aprosodia The inability to infuse language with its normal emotional content.

arachnoid mater One of the three coverings of the brain that make up the meninges; lies between the dura mater and the pia mater.

areflexia Loss of reflexes.

association cortex Defined by exclusion as those neocortical regions that are not involved in primary sensory or motor processing.

associativity In the hippocampus, the enhancement of a weakly activated group of synapses when a nearby group is strongly activated.

astrocytes One of the three major classes of glial cells found in the central nervous system; important in regulating the ionic milieu of nerve cells and, in some cases, transmitter reuptake.

astrotactin A cell surface molecule that causes neurons to adhere to radial glial fibers during neuronal migration.

athetosis Slow, writhing movements seen primarily in patients with disorders of the basal ganglia.

ATPase pumps Membrane pumps that use the hydrolysis of ATP to translocate ions against their electrochemical gradients.

atrophy The physical wasting away of a tissue, typically muscle, in response to disuse or other causes.

attention The selection of a particular sensory stimulus or mental process for further analysis.

auditory meatus Opening of the external ear canal.

auditory space map Topographic representation of sound source location, as occurs in the inferior colliculus.

autonomic nervous system The components of the nervous system (peripheral and central) concerned with the regulation of smooth muscle, cardiac muscle, and glands (see also visceral motor system).

axon The neuronal process that carries the action potential from the nerve cell body to a target.

axoplasmic transport The process by which materials are carried from nerve cell bodies to their terminals (anterograde transport), or from nerve cell terminals to the neuronal cell body (retrograde transport).

baroreceptors Sensory receptors in the visceral motor system that respond to changes in blood pressure.

basal ganglia A group of nuclei lying deep in the subcortical white matter of the frontal lobes that organize motor behavior. The caudate and putamen and the globus pallidus are the major components of the basal ganglia; the subthalamic nucleus and substantia nigra are often included.

basal lamina (basement membrane) A thin layer of extracellular matrix material (primarily collagen, laminin, and fibronectin) that surrounds muscle cells and Schwann cells. Also underlies all epithelial sheets.

basilar membrane The membrane that forms the floor of the cochlear duct, on which the cochlear hair cells are located.

basket cells Inhibitory interneurons in the cerebellar cortex whose cells bodies are located within the Purkinje cell layer and whose axons make basketlike terminal arbors around Purkinje cell bodies.

binocular Referring to both eyes.

biogenic amines The bioactive amine neurotransmitters; includes the catecholamines (epinephrine, norepinephrine, dopamine), serotonin, and histamine.

bipolar cells Retinal neurons that provide a direct link between photoreceptor terminals and ganglion cell dendrites.

bisexuality Sexual attraction to members of both the opposite and the same phenotypic sex.

blastomere A cell produced when the egg undergoes cleavage.

blastula An early embryo during the stage when the cells are typically arranged to form a hollow sphere.

blind spot The region of visual space that falls on the optic disk; due to the lack of photoreceptors in the optic disk, objects that lie completely within the blind spot are not perceived.

blood-brain barrier A diffusion barrier between the brain vasculature and the substance of the brain formed by tight junctions between capillary endothelial cells.

bouton (synaptic bouton) A swelling specialized for the release of neurotransmitter that occurs along or at the end of an axon.

bradykinesia Pathologically slow movement.

brain-derived neutrophic factor (BDNF) One member of a family of neutrophic factors, the best-known constituent of which is nerve growth factor.

brainstem The portion of the brain that lies between the diencephalon and the spinal cord; comprises the midbrain, pons, and medulla.

Broca's aphasia Difficulty producing speech as a result of damage to Broca's area in the left frontal lobe.

Broca's area An area in the left frontal lobe specialized for the production of language.

CA1 A region of the hippocampus that shows a robust form of long-term potentiation.

CA3 A region of the hippocampus containing the neurons that form the Schaffer collaterals.

cadherins A family of calcium-dependent cell adhesion molecules found on the surfaces of growth cones and the cells over which they grow.

calcarine sulcus The major sulcus on the medial aspect of the occipital lobe; the primary visual cortex lies largely within this sulcus.

cAMP response element binding protein (CREB) A protein activated by cyclic AMP that binds to specific regions of DNA, thereby increasing the transcription rates of nearby genes.

cAMP response elements (CREs) Specific DNA sequences that bind transcription factors activated by cAMP (see also cAMP response element binding protein).

carotid bodies Specialized tissue masses found at the bifurcation of the carotid arteries in humans and other mammals that respond to the chemical composition of the blood (primarily the partial pressure of oxygen and carbon dioxide).

catecholamine A term referring to molecules containing a catechol ring and an amino group; examples are the neurotransmitters epinephrine, norepinephrine, and dopamine.

cauda equina The collection of segmental ventral and dorsal roots that extend from the caudal end of the spinal cord to their exit from the spinal canal.

caudal Posterior, or "tailward."

caudate nucleus One of the three major components of the basal ganglia (the other two are the globus pallidus and putamen).

cell adhesion molecules A family of molecules on cell surfaces that cause them to stick to one another (see also fibronectin and laminin).

central nervous system The brain and spinal cord of vertebrates (by analogy, the central nerve cord and ganglia of invertebrates).

central pattern generator Oscillatory spinal cord or brainstem circuits responsible for programmed, rhythmic movements such as locomotion.

central sulcus A major sulcus on the lateral aspect of the hemispheres that forms the boundary between the frontal and parietal lobes. The anterior bank of the sulcus contains the primary motor cortex; the posterior bank contains the primary sensory cortex.

cerebellar ataxia A pathological inability to make coordinated movements associated with lesions to the cerebellum.

cerebellar cortex The superficial gray matter of the cerebellum.

cerebellar peduncles The three bilateral pairs of axon tracts (inferior, middle, and superior cerebellar peduncles) that carry information to and from the cerebellum.

cerebellum Prominent hindbrain structure concerned with motor coordination, posture, and balance. Composed of a three-layered cortex and deep nuclei; attached to the brainstem by the cerebellar peduncles.

cerebral aqueduct The portion of the ventricular system that connects the third and fourth ventricles.

cerebral cortex The superficial gray matter of the cerebral hemispheres.

cerebral peduncles The major fiber bundles that connect the brainstem to the cerebral hemispheres.

cerebrocerebellum The part of the cerebellar cortex that receives input from the cerebral cortex via axons from the pontine relay nuclei.

cerebrospinal fluid A normally clear and cell-free fluid that fills the ventricular system of the central nervous system; produced by the choroid plexus in the third ventricle.

cerebrum The largest and most rostral part of the brain in humans and other mammals, consisting of the two cerebral hemispheres.

c-fos Cellular Feline Osteosarcoma gene product; a transcription factor that binds as a heterodimer, thus activating gene transcription.

chemical synapses Synapses that transmit information via the secretion of chemical signals (neurotransmitters).

chemoaffinity (chemoaffinity hypothesis) The idea that nerve cells bear chemical labels that determine their connectivity.

chemotaxis The movement of a cell up (or down) the gradient of a chemical signal.

chemotropism The growth of a part of a cell (axon, dendrite, filopodium) up (or down) a chemical gradient.

chimera An experimentally generated embryo (or organ) comprising cells derived from two or more species (or other genetically distinct sources).

cholinergic Referring to synaptic transmission mediated by acetylcholine.

chorea Jerky, involuntary movements of the face or extremities associated with damage to the basal ganglia.

choreoathetosis The combination of jerky, ballistic, and writhing movements that characterizes the late stages of Huntington's disease.

choroid plexus Specialized epithelium in the ventricular system that produces cerebrospinal fluid.

chromosome Nuclear organelle that bears the genes.

ciliary body Circular band of muscle surrounding the lens; contraction allows the lens to round up during accommodation.

cingulate cortex Cortex of the cingulate gyrus that surrounds the corpus callosum; important in emotional and visceral motor behavior.

cingulate gyrus Prominent gyrus on the medial aspect of the hemisphere, lying just superior to the corpus callosum; forms a part of the limbic system.

cingulate sulcus Prominent sulcus on the medial aspect of the hemisphere.

circadian rhythms Variations in physiological functions that occur on a daily basis.

circle of Willis Arterial anastomosis on the ventral aspect of the midbrain; connects the posterior and anterior cerebral circulation.

cisterns Large, cerebrospinal-fluid-filled spaces that lie within the subarachnoid space.

class A taxonomic category subordinate to phylum; comprises animal orders.

climbing fibers Axons that originate in the inferior olive, ascend through the inferior cerebellar peduncle, and make terminal arborizations that invest the dendritic tree of Purkinje cells.

clone The progeny of a single cell.

cochlea The coiled structure within the inner ear where vibrations caused by sound are transduced into neural impulses.

cognition A general term referring to higher order mental processes; the ability of the central nervous system to attend, identify, and act on complex stimuli.

collapsin A molecule that causes collapse of growth cones; a member of the semaphorin family of signaling molecules.

colliculi The two paired hillocks that characterize the dorsal surface of the midbrain; the superior colliculi concern vision, the inferior colliculi audition.

competition The struggle among nerve cells, or nerve cell processes, for limited resources essential to survival or growth.

concha A component of the external ear.

conduction aphasia Difficulty producing speech as a result of damage to the connection between Wernicke's and Broca's language areas.

conduction velocity The speed at which an action potential is propagated along an axon.

conductive hearing loss Diminished sense of hearing due reduced ability of sounds to be mechanically transmitted to the inner ear. Common causes include occlusion of the ear canal, perforation of the tympanic membrane, and arthritic degeneration of the middle ear ossicles. Contrast with sensorineural hearing loss.

cone opsins The three distinct photopigments found in cones; the basis for color vision.

cones Photoreceptors specialized for high visual acuity and the perception of color.

congenital adrenal hyperplasia Genetic deficiency that leads to overproduction of androgens and a resultant masculinization of external genitalia in genotypic females.

conjugate The paired movements of the two eyes in the same direction, as occurs in the vestibulo-ocular reflex (see also vergence movements and vestibulo-ocular reflex).

conspecific Fellow member of a species.

contralateral On the other side.

contralateral neglect syndrome Neurological condition in which the patient does not acknowledge or attend to the left visual hemifield or the left half of the body. The syndrome typically results from lesions of the right parietal cortex.

contrast The difference, usually expressed in terms of a percentage in luminance, between two territories in the visual field (can also apply to color when specified as spectral contrast).

convergence Innervation of a target cell by axons from more than one neuron.

cornea The transparent surface of the eyeball in front of the lens; the major refractive element in the optical pathway.

coronal Referring to a plane through the brain that runs parallel to the coronal suture (the mediolateral plane). Synonymous with frontal plane.

corpus callosum The large midline fiber bundle that connects the cortices of the two cerebral hemispheres.

corpus striatum General term applied to the caudate and putamen; name derives from the striated appearance of these basal ganglia nuclei in sections of fresh material.

cortex The superficial mantle of gray matter covering the cerebral hemispheres and cerebellum, where most of the neurons in the brain are located.

cortico-cortical connections Connections made between cortical areas in the same hemisphere or betweem the two hemispheres via the cerebral commissures (the corpus callosum and the anterior commissure).

corticospinal tract Pathway carrying motor information from the primary and secondary motor cortices to the brain stem and spinal cord.

co-transmitters Two or more types of neurotransmitters within a single synapse; may be packaged into separate populations of synaptic vesicles or co-localized within the same synaptic vesicles.

cranial nerve ganglia The sensory ganglia associated with the cranial nerves; these correspond to the dorsal root ganglia of the spinal segmental nerves.

cranial nerve nuclei Nuclei in the brainstem that contain the neurons related to cranial nerves III–XII.

cranial nerves The 12 pairs of nerves arising from the brainstem that carry sensory information toward (and sometimes motor information away from) the central nervous system.

CREB see cAMP response element binding protein.

crista The hair cell-containing sensory epithelium of the semicircular canals.

critical period A restricted developmental period during which the nervous system is particularly sensitive to the effects of experience.

cuneate nuclei Sensory relay nuclei that lie in the lower medulla; they contain the second-order sensory neurons that relay mechanosensory information from peripheral receptors in the upper body to the thalamus.

cupulae Gelatinous structures in the semicircular canals in which the hair cell bundles are embedded.

cytoarchitectonic areas Distinct regions of the neocortical mantle identified by differences in cell size, packing density, and laminar arrangement.

decerebrate rigidity Excessive tone in extensor muscles as a result of damage to descending motor pathways at the level of the brainstem.

declarative memory Memories available to consciousness that can be expressed by language.

decussation A crossing of fiber tracts in the midline.

deep cerebellar nuclei The nuclei at the base of the cerebellum that relay information from the cerebellar cortex to the thalamus.

delayed response genes Genes that are synthesized de novo after a cell is stimulated; usually refers to transcriptional activator proteins that are synthesized after preexisting transcription factors are first activated by an inducing stimulus.

delayed response task A behavioral paradigm used to test cognition and memory.

delta waves Slow (<4 Hz) electroencephalographic waves that characterize stage IV (slow-wave) sleep.

dendrite A neuronal process arising from the cell body that receives synaptic input.

denervation Removal of the innervation to a target.

dentate gyrus A region of the hippocampus; so named because it is shaped like a tooth.

depolarization The displacement of a cell's membrane potential toward a less negative value.

dermatome The area of skin supplied by the sensory axons of a single spinal nerve.

determination Commitment of a developing cell or cell group to a particular fate.

dichromatic Referring to the majority of mammals (and most color-blind humans), which have only two instead of three cone pigments to mediate color vision.

diencephalon Portion of the brain that lies just rostral to the midbrain; comprises the thalamus and hypothalamus.

differentiation The progressive specialization of developing cells.

dihydrotestosterone A more potent form of testosterone that masculinizes the external genitalia.

disinhibition Arrangement of inhibitory and excitatory cells in a circuit that generates excitation by the transient inhibition of a tonically active inhibitory neuron.

disjunctive eye movements Movements of the two eyes in opposite directions (see also vergence movements).

distal Farther away from a point of reference (the opposite of proximal).

divergence The branching of an axon to innervate multiple target cells.

dopamine A catecholamine neurotransmitter.

dorsal Referring to the back.

dorsal column nuclei Second-order sensory neurons in the lower medulla that relay mechanosensory information from the spinal cord to the thalamus; comprises the cuneate and gracile nuclei.

dorsal columns Major ascending tracts in the spinal cord that carry mechanosensory information from the first-order sensory neurons in dorsal root ganglia to the dorsal column nuclei; also called the posterior funiculi.

dorsal horn The dorsal portion of the spinal cord gray matter; contains neurons that process sensory information.

dorsal root ganglia (DRG) The segmental sensory ganglia of the spinal cord; contain the first-order neurons of the dorsal column/medial lemniscus and spinothalamic pathways.

dorsal roots The bundle of axons that runs from the dorsal root ganglia to the dorsal horn of the spinal cord, carrying sensory information from the periphery.

dura mater The thick external covering of the brain and spinal cord; one of the three components of the meninges, the other two being the pia mater and arachnoid mater.

dynorphins A class of endogenous opioid peptides.

dysarthria Difficulty producing speech as a result of damage to the primary motor centers that govern the muscles of articulation; distinguished from aphasia, which results from cortical damage.

dysmetria Inaccurate movements due to faulty judgment of distance. Characteristic of cerebellar pathology.

dystonia Lack of muscle tone.

early inward current The initial electrical current, measured in voltage clamp experiments, that results from the voltage-dependent entry of a cation such as Na^+ or Ca^{2+}; produces the rising phase of the action potential.

ectoderm The most superficial of the three embryonic germ layers; gives rise to the nervous system and epidermis.

Edinger-Westphal nucleus Midbrain nucleus containing the autonomic neurons that constitute the efferent limb of the pupillary light reflex.

efferent An axon that conducts information away from the central nervous system.

electrical synapses Synapses that transmit information via the direct flow of electrical current at gap junctions.

electrochemical equilibrium The condition in which no net ionic flux occurs across a membrane because ion concentration gradients and opposing transmembrane potentials are in exact balance.

electrogenic Capable of generating an electrical current; usually applied to membrane transporters that create electrical currents while translocating ions.

embryo The developing organism before birth or hatching.

end plate current (EPC) Postsynaptic current produced by neurotransmitter release and binding at the motor end plate.

end plate potential (EPP) Depolarization of the membrane potential of skeletal muscle fiber, caused by the action of the transmitter acetylcholine at the neuromuscular synapse.

endocrine Referring to the release of signaling molecules whose effects are made widespread by distribution in the general circulation.

endocytosis A budding off of vesicles from the plasma membrane, which allows uptake of materials in the extracellular medium.

endoderm The innermost of the three embryonic germ layers.

endogenous opioids Peptides in the central nervous system that have the same pharmacological effects as morphine and other derivatives of opium.

endolymph The potassium-rich fluid filling both the cochlear duct and the membranous labyrinth; bathes the apical end of the hair cells.

endorphins One of a group of neuropeptides that are agonists at opioid receptors, virtually all of which contain the sequence Tyr-Gly-Gly-Phe.

end plate The complex postsynaptic specialization at the site of nerve contact on skeletal muscle fibers.

engram The term used to indicate the physical basis of a stored memory.

enkephalins A general term for endogenous opioid peptides.

ependyma The epithelial lining of the canal of the spinal cord and the ventricles.

ependymal cells Epithelial cells that line the ventricular system.

epidermis The outermost layer of the skin; derived from the embryonic ectoderm.

epigenetic Referring to influences on development that arise from factors other than genetic instructions.

epinephrine (adrenaline) Catecholamine hormone and neurotransmitter that binds to α- and β-adrenergic G-protein-coupled receptors.

epineurium The connective tissue surrounding axon fascicles of a peripheral nerve.

epithelium Any continuous layer of cells that covers a surface or lines a cavity.

equilibrium potential The membrane potential at which a given ion is in electrochemical equilibrium.

estradiol One of the biologically important C_{18} class of steroid hormones capable of inducing estrous in females.

eukaryote An organism that contains cells with nuclei.

excitatory postsynaptic potential (EPSP) Neurotransmitter-induced postsynaptic potential change that depolarizes the cell, and hence increases the likelihood of initiating a postsynaptic action potential.

exocytosis A form of cell secretion resulting from the fusion of the membrane of a storage organelle, such as a synaptic vesicle, with the plasma membrane.

explant A piece of tissue maintained in culture medium.

external segment A subdivision of the globus pallidus.

extracellular matrix A matrix composed of collagen, laminin, and fibronectin that surrounds most cells (see also basal lamina).

extrafusal muscle fibers Fibers of skeletal muscles; a term that distinguishes ordinary muscle fibers from the specialized intrafusal fibers associated with muscle spindles.

face cells Neurons in the temporal cortex of rhesus monkeys that respond specifically to faces.

facilitation The increased transmitter release produced by an action potential that follows closely upon a preceding action potential.

family A taxonomic category subordinate to order; comprises genera.

fasciculation The aggregation of neuronal processes to form a nerve bundle; also refers to the spontaneous discharge of motor units after muscle denervation.

α-fetoprotein A protein that actively sequestors circulating estrogens.

fetus The developing mammalian embryo at relatively late stages when the parts of the body are recognizable.

fibrillation Spontaneous contractile activity of denervated muscle fibers.

fibroblast growth factor (FGF) A peptide growth factor, originally defined by its mitogenic effects on fibroblasts; also acts as an inducer during early brain development.

fibronectin A large cell adhesion molecule that binds integrins.

filopodium Slender protoplasmic projection, arising from the growth cone of an axon or a dendrite, that explores the local environment.

fissure A deep cleft in the brain; distinguished from sulci, which are shallower cortical infoldings.

flexion reflex Polysynaptic reflex mediating withdrawal from a painful stimulus.

floorplate Region in the ventral portion of the developing spinal cord; important in the guidance and crossing of growing axons.

folia The name given to the gyral formations of the cerebellum.

forebrain The anterior portion of the brain that includes the cerebral hemispheres (includes the telencephalon and diencephalon).

fornix An axon tract, best seen from the medial surface of the divided brain, that interconnects the hypothalamus and hippocampus.

fourth ventricle The ventricular space that lies between the pons and the cerebellum.

fovea Area of the retina specialized for high acuity in the center of the macula; contains a high density of cones and few rods.

foveola Capillary and rod-free zone in the center of the fovea.

frontal lobe One of the four lobes of the brain; includes all the cortex that lies anterior to the central sulcus and superior to the lateral fissure.

G-protein-coupled receptors (metabotropic receptors) A large family of neurotransmitter or hormone receptors, characterized by seven transmembrane domains; the binding of these receptors by agonists leads to the activation of intracellular G-proteins.

G-proteins Term for two large groups of proteins—the heterotrimeric G-proteins and the small-molecule G-proteins—that can be activated by exchanging bound GDP for GTP.

gamma (γ) motor neurons Class of spinal motor neurons specifically concerned with the regulation of muscle spindle length; these neurons innervate the intrafusal muscle fibers of the spindle.

ganglion (plural, ganglia) Collections of hundreds to thousands of neurons found outside the brain and spinal cord along the course of peripheral nerves.

ganglion cell A neuron located in a ganglion.

gap junction A specialized intercellular contact formed by channels that directly connect the cytoplasm of two cells.

gastrula The early embryo during the period when the three embryonic germ layers are formed; follows the blastula stage.

gastrulation The cell movements (invagination and spreading) that transform the embryonic blastula into the gastrula.

gender identification Self-perception of one's alignment with the traits associated with being a phenotypic female or male in a given culture.

gene A hereditary unit located on the chromosomes; genetic information is carried by linear sequences of nucleotides in DNA that code for corresponding sequences of amino acids.

genome The complete set of an animal's genes.

genotype The genetic makeup of an individual.

genotypic sex Sexual characterization according to the complement of sex chromosomes; XX is a genotypic female, and XY is a genotypic male.

genus A taxonomic division that comprises a number of closely related species within a family.

germ cell The egg or sperm (or the precursors of these cells).

germ layers The three primary layers of the developing embryo from which all adult tissues arise: ectoderm, mesoderm, and endoderm.

glia (neuroglial cells) The support cells associated with neurons (astrocytes, oligodendrocytes, and microglia in the central nervous system; Schwann cells in peripheral nerves; and satellite cells in ganglia).

globus pallidus One of the three major nuclei that make up the basal ganglia in the cerebral hemispheres; relays information from the caudate and putamen to the thalamus.

glomeruli Characteristic collections of neuropil in the olfactory bulbs; formed by dendrites of mitral cells and terminals of olfactory receptor cells, as well as processes from local interneurons.

glutamate-glutamine cycle A metabolic cycle of glutamate release and resynthesis involving both neuronal and glial cells.

G_{olf} A G-protein found uniquely in olfactory receptor neurons.

Golgi tendon organs Receptors located in muscle tendons that provide mechanosensory information to the central nervous system about muscle tension.

gracile nuclei Sensory nuclei in the lower medulla; these second-order sensory neurons relay mechanosensory information from the lower body to the thalamus.

gradient A systematic variation of the concentration of a molecule (or some other agent) that influences cell behavior.

granule cell layer The layer of the cerebellar cortex where granule cell bodies are found. Also used to refer to cell-rich layers in neocortex and hippocampus.

gray matter General term that describes regions of the central nervous system rich in neuronal cell bodies and neuropil; includes the cerebral and cerebellar cortices, the nuclei of the brain, and the central portion of the spinal cord.

Green Fluorescent Protein (GFP) A protein, originally discovered in a light-emitting jellyfish, that generates green fluorescent light. GFP is widely used as a genetic tag in fluorescence microscopy. It allows observation of specific neurons and some of their components over time in living cells, or even in whole organisms. Especially exciting has been the ability to monitor changes neuronal structure over time.

growth cone The specialized end of a growing axon (or dendrite) that generates the motive force for elongation.

gyri The ridges of the infolded cerebral cortex (the valleys between these ridges are called sulci).

hair cells The sensory cells within the inner ear that transduce mechanical displacement into neural impulses.

helicotrema The opening at the apex of the cochlea that joins the scala vestibuli and scala tympani.

Hensen's node see primitive pit.

heterotrimeric G-proteins A large group of proteins consisting of three subunits (α, β, and γ) that can be activated by exchanging bound GDP with GTP resulting in the liberation of two signaling molecules—αGTP and the βγ-dimer.

higher-order neurons Neurons that are relatively remote from peripheral targets.

hindbrain see rhombencephalon.

hippocampus A cortical structure in the medial portion of the temporal lobe; in humans, concerned with short-term declarative memory, among many other functions.

histamine A biogenic amine neurotransmitter derived from the amino acid histidine.

homeobox genes A set of master control genes whose expression establishes the early body plan of developing organisms (see also homeotic mutant).

homeotic mutant A mutation that transforms one part of the body into another (e.g., insect antennae into legs). Affects homeobox genes.

homologous Technically, referring to structures in different species that share the same evolutionary history; more generally, referring to structures or organs that have the same general anatomy and perform the same function.

homosexuality Sexual attraction to an individual of the same phenotypic sex.

horizontal cells Retinal neurons that mediate lateral interactions between photoreceptor terminals and the dendrites of bipolar cells.

horseradish peroxidase A plant enzyme widely used to stain nerve cells (after injection into a neuron, it generates a visible precipitate by one of several histochemical reactions).

Huntington's disease An autosomal dominant genetic disorder in which a single gene mutation results in personality changes, progressive loss of the control of voluntary movement, and eventually death. Primary target is the basal ganglia.

hydrocephalus Enlarged cranium as a result of increased cerebrospinal fluid pressure (typically due to a mechanical outflow blockage).

hyperalgesia Increased perception of pain.

hyperkinesia Excessive movement.

hyperpolarization The displacement of a cell's membrane potential toward a more negative value.

hypokinesia A paucity of movement.

hypothalamus A collection of small but critical nuclei in the diencephalon that lies just inferior to the thalamus; governs reproductive, homeostatic, and circadian functions.

imprinting A rapid and permanent form of learning that occurs in response to early experience.

inactivation The time-dependent closing of ion channels in response to a stimulus, such as membrane depolarization.

inducers Chemical signals originating from one set of cells that influence the differentiation of other cells.

induction The ability of a cell or tissue to influence the fate of nearby cells or tissues during development by chemical signals.

inferior colliculi (singular, colliculus) Paired hillocks on the dorsal surface of the midbrain; concerned with auditory processing.

inferior olive (inferior olivary nucleus) Prominent nucleus in the medulla; a major source of input to the cerebellum.

infundibulum The connection between the hypothalamus and the pituitary gland; also known as the pituitary stalk.

inhibitory postsynaptic potential (IPSP) Neurotransmitter-induced postsynaptic potential change that tends to decrease the likelihood of a postsynaptic action potential.

innervate Establish synaptic contact with a target.

innervation Referring to all the synaptic contacts of a target.

input The innervation of a target cell by a particular axon; more loosely, the innervation of a target.

input elimination The developmental process by which the number of axons innervating some classes of target cells is diminished.

instructive A developmental influence that dictates the fate of a cell rather than simply permitting differentiation to occur.

insula The portion of the cerebral cortex that is buried within the depths of the lateral fissure.

integral membrane proteins Proteins that possess hydrophobic domains that are inserted into membranes.

integration The summation of excitatory and inhibitory synaptic conductance changes by postsynaptic cells.

integrins A family of receptor molecules found on growth cones that bind to cell adhesion molecules such as laminin and fibronection.

intention tremor Tremor that occurs while performing a voluntary motor act. Characteristic of cerebellar pathology.

internal arcuate tract Mechanosensory pathway in the brainstem that runs from the dorsal column nuclei to form the medial lemniscus.

internal capsule Large white matter tract that lies between the diencephalon and the basal ganglia; contains, among others, sensory axons that run from the thalamus to the cortex and motor axons that run from the cortex to the brainstem and spinal cord.

interneuron Technically, a neuron in the pathway between primary sensory and primary effector neurons; more generally, a neuron that branches locally to innervate other neurons.

interstitial nuclei of the anterior hypothalamus (INAH) Four cell groups located slightly lateral to the third ventricle in the anterior hypothalamus of primates; thought to play a role in sexual behavior.

intrafusal muscle fibers Specialized muscle fibers found in muscle spindles.

invertebrate An animal without a backbone (includes about 97% of extant animals).

in vitro Referring to any biological process studied outside of the organism (literally, "in glass").

in vivo Referring to any biological process studied in an intact living organism (literally "in life").

ion channels Integral membrane proteins possessing pores that allow certain ions to diffuse across cell membranes, thereby conferring selective ionic permeability.

ion exchangers Membrane transporters that translocate one or more ions against their concentration gradient by using the electrochemical gradient of other ions as an energy source.

ionotropic (ionotropic receptors) Receptors in which the ligand binding site is an integral part of the receptor molecule.

ion pumps see transporters.

ipsilateral On the same side of the body.

iris Circular pigmented membrane behind the cornea; perforated by the pupil.

ischemia Insufficient blood supply.

kinocilium A true ciliary structure which, along with the stereocilia, comprises the hair bundle of vestibular and fetal cochlear hair cells in mammals (it is not present in the adult mammalian cochlear hair cell).

Korsakoff's syndrome An amnesic syndrome seen in chronic alcoholics.

labyrinth Referring to the internal ear; comprises the cochlea, vestibular apparatus, and the bony canals in which these structures are housed.

lamellipodia The leading edge of a motile cell or growth cone, which is rich in actin filaments.

laminae (singular, lamina) Cell layers that characterize the neocortex, hippocampus, and cerebellar cortex. The gray matter of the spinal cord is also arranged in laminae.

laminin A large cell adhesion molecule that binds integrins.

late outward current The delayed electrical current, measured in voltage clamp experiments, that results from the voltage-dependent efflux of a cation such as K^+. Produces the repolarizing phase of the action potential.

lateral columns The lateral regions of spinal cord white matter that convey motor information from the brain to the spinal cord.

lateral (Sylvian) fissure The cleft on the lateral surface of the brain that separates the temporal and frontal lobes.

lateral geniculate nucleus (LGN) A nucleus in the thalamus that receives the axonal projections of retinal ganglion cells in the primary visual pathway.

lateral olfactory tract The projection from the olfactory bulbs to higher olfactory centers.

lateral posterior nucleus A thalamic nucleus that receives its major input from sensory and association cortices and projects in turn to association cortices, particularly in the parietal and temporal lobes.

lateral superior olive (LSO) The auditory brainstem structure that processes interaural intensity differences and, in humans, mediates sound localization for stimuli greater than 3 kHz.

learning The acquisition of novel behavior through experience.

lens Transparent structure in the eye whose thickening or flattening in response to visceral motor control allows light rays to be focused on the retina.

lexical The quality of associating a symbol (e.g., a word) with a particular object, emotion, or idea.

lexicon Dictionary. Sometimes used to indicate region of brain that stores the meanings of words.

ligand-gated ion channels Term for a large group of neurotransmitter receptors that combine receptor and ion channel functions into a single molecule.

limb bud The limb rudiment of vertebrate embryos.

limbic lobe Cortex that lies superior to the corpus callosum on the medial aspect of the cerebral hemispheres; forms the cortical component of the limbic system.

limbic system Term that refers to those cortical and subcortical structures concerned with the emotions; the most prominent components are the cingulate gyrus, the hippocampus, and the amygdala.

lobes The four major divisions of the cerebral cortex (frontal, parietal, occipital, and temporal).

local circuit neurons General term referring to neurons whose activity mediates interactions between sensory systems and motor systems; interneuron is often used as a synonym.

locus coeruleus A small brainstem nucleus with widespread adrenergic cortical and descending connections; important in the governance of sleep and waking.

long-term Lasting days, weeks, months, or longer.

long-term depression A persistent weakening of synapses based on recent patterns of activity.

long-term memory Memories that last days, weeks, months, years, or a lifetime.

long-term potentiation (LTP) A persistent strengthening of synapses based on recent patterns of activity.

lower motor neuron Spinal motor neuron; directly innervates muscle (also referred to as α or primary motor neuron).

lower motor neuron syndrome Signs and symptoms arising from damage to α motor neurons; these include paralysis or paresis, muscle atrophy, areflexia, and fibrillations.

macroscopic Visible with the naked eye.

macroscopic currents Ionic currents flowing through large numbers of ion channels distributed over a substantial area of membrane.

macula The central region of the retina that contains the fovea (the term derives from the yellowish appearance of this region in ophthalmoscopic examination); also, the sensory epithelia of the otolith organs.

magnocellular A component of the primary visual pathway specialized for the perception of motion; so named because of the relatively large cells involved.

mammal An animal the embyros of which develop in a uterus and the young of which begin to suckle at birth (technically, a member of the class Mammalia).

mammillary bodies Small prominences on the ventral surface of the diencephalon; functionally, part of the caudal hypothalamus.

map The ordered projection of axons from one region of the nervous system to another, by which the organization of the body (or some function) is reflected in the organization of the nervous system.

mechanoreceptors Receptors specialized to sense mechanical forces.

medial Located nearer to the midsagittal plane of an animal (the opposite of lateral).

medial dorsal nucleus A thalamic nucleus that receives its major input from sensory and association cortices and projects in turn to association cortices, particularly in the frontal lobe.

medial geniculate complex The major thalamic relay for auditory information.

medial lemniscus Axon tract in the brainstem that carries mechanosensory information from the dorsal column nuclei to the thalamus.

medial longitudinal fasciculus Axon tract that carries excitatory projections from the abducens nucleus to the contralateral oculomotor nucleus; important in coordinating conjugate eye movements.

medial superior olive (MSO) The auditory brainstem structure that processes interaural time differences and serves to compute the horizontal location of a sound source.

medium spiny neuron The principal projection neuron of the caudate and putamen.

medulla The caudal portion of the brainstem, extending from the pons to the spinal cord.

meduallary pyramids Longitudinal bulges on the ventral aspect of the medulla that signify the corticospinal tracts at this level of the neuraxis.

Meissner's corpuscles Encapsulated cutaneous mechanosensory receptors specialized for the detection of fine touch and pressure.

membrane conductance The reciprocal of membrane resistance. Changes in membrane conductance result from, and are used to describe, the opening or closing of ion channels.

meninges The external covering of the brain; includes the pia, arachnoid, and dura mater.

Merkel's disks Encapsulated cutaneous mechanosensory receptors specialized for the detection of fine touch and pressure.

mesencephalon see midbrain.

mesoderm The middle of the three germ layers; gives rise to muscle, connective tissue, skeleton, and other structures.

mesopic Light levels at which both the rod and cone systems are active.

metabotropic (metabotropic receptors) Refers to receptors that are indirectly activated by the action of neurotransmitters or other extracellular signals, typically through the aegis of G-protein activation.

Meyer's loop That part of the optic radiation that runs in the caudal portion of the temporal lobe.

microglial cells One of the three main types of central nervous system glia; concerned primarily with repairing damage following neural injury.

microscopic currents Ionic currents flowing through single ion channels.

midbrain (mesencephalon) The most rostral portion of the brainstem; identified by the superior and inferior colliculi on its dorsal surface, and the cerebral penduncles on its ventral aspect.

middle cerebellar peduncle Large white matter tract that carries axons from the pontine relay nuclei to the cerebellar cortex.

miniature end plate potential (MEPP) Small, spontaneous depolarization of the membrane potential of skeletal muscle cells, caused by the release of a single quantum of acetylcholine.

mitral cells The major output neurons of the olfactory bulb.

mnemonic Having to do with memory.

modality A category of function. For example, vision, hearing, and touch are different sensory modalities.

molecular layer The layer of the cerebellar cortex containing the apical dendrites of Purkinje cells, parallel fibers from granule cells, a few local circuit neurons, and the synapses between these elements.

monoclonal antibody An antibody molecule raised from a clone of transformed lymphocytes.

morphine A plant alkaloid that gives opium its analgesic properties.

morphogen A molecule that influences morphogenesis.

morphogenesis The generation of animal form.

morphology The study of the form and structure of organisms; or, more commonly, the form and structure of an animal or animal part.

motor Pertaining to movement.

motor cortex The region of the cerebral cortex lying anterior to the central sulcus concerned with motor behavior; includes the primary motor cortex in the precentral gyrus and associated cortical areas in the frontal lobe.

motor neuron By usage, a nerve cell that innervates skeletal muscle. Also called primary or α motor neuron.

motor neuron pool The collection of motor neurons that innervates a single muscle.

motor system A broad term used to describe all the central and peripheral structures that support motor behavior.

motor unit A motor neuron and the skeletal muscle fibers it innervates; more loosely, the collection of skeletal muscle fibers innervated by a single motor neuron.

mucosa Term referring the mucus membranes lining the nose, mouth, gut, and other epithelial surfaces.

muscarinic receptors A group of G-protein-coupled acetylcholine receptors activated by the plant alkaloid muscarine.

muscle spindle Highly specialized sensory organ found in most skeletal muscles; provides mechanosensory information about muscle length.

muscle tone The normal, ongoing tension in a muscle; measured by resistance of a muscle to passive stretching.

myelin The multilaminated wrapping around many axons formed by oligodendrocytes or Schwann cells.

myelination Process by which glial cells wrap axons to form multiple layers of glial cell membrane that increase axonal conduction velocity.

myotatic reflex (stretch reflex) A fundamental spinal reflex that is generated by the motor response to afferent sensory information arising from muscle spindles.

myotome The part of each somite that contributes to the development of skeletal muscles.

Na^+/K^+ transporter (or Na^+ pump) A type of ATPase transporter in the plasma membrane of most cells that is responsible for accumulating intracellular K^+ and extruding intracellular Na^+.

nasal (nasal division) Referring to the region of the visual field of each eye in the direction of the nose.

near reflex Reflexive response induced by changing binocular fixation to a closer target; includes convergence, accommodation, and pupillary constriction.

neocortex The six-layered cortex that forms the surface of most of the cerebral hemispheres.

Nernst equation A mathematical relationship that predicts the equilibrium potential across a membrane that is permeable to only one ion.

nerve A collection of peripheral axons that are bundled together and travel a common route.

nerve growth factor (NGF) A neurotrophic protein required for survival and differentiation of sympathetic ganglion cells and certain sensory neurons. Preeminent member of the neurotrophin family of growth factors.

netrins A family of diffusible molecules that act as attractive or repulsive cues to guide growing axons.

neural cell adhesion molecule (N-CAM) Molecule that helps bind axons together and is widely distributed in the developing nervous system. Structurally related to immunoglobin.

neural crest A group of progenitor cells that forms along the dorsum of the neural tube and gives rise to peripheral neurons and glia (among other derivatives).

neural plate The thickened region of the dorsal ectoderm of a neurula that gives rise to the neural tube.

neural tube The primordium of the brain and spinal cord; derived from the neural ectoderm.

neurite A neuronal branch (usually used when the process in question could be either an axon or a dendrite, such as the branches of isolated nerve cells in tissue culture).

neuroblast A dividing cell, the progeny of which develop into neurons.

neurogenesis The development of the nervous system.

neuroglial cells see glia.

neuroleptics A group of antipsychotic agents that cause indifference to stimuli by blocking brain dopamine receptors.

neuromere A segment of the rhombencephalon (synonym for rhombomere).

neuromuscular junction The synapse made by a motor axon on a skeletal muscle fiber.

neuron Cell specialized for the conduction and transmission of electrical signals in the nervous system.

neuronal geometry The spatial arrangement of neuronal branches.

neuron-glia cell adhesion molecule (Ng-CAM) A cell adhesion molecule, structurally related to immunoglobin molecules, that promotes adhesive interactions between neurons and glia.

neuropeptides A general term describing a large number of peptides that function as neurotransmitters or neurohormones.

neuropil The dense tangle of axonal and dendritic branches, and the synapses between them, that lies between neuronal cell bodies in the gray matter of the brain and spinal cord.

neurotransmitter Substance released by synaptic terminals for the purpose of transmitting information from one nerve cell to another.

neurotrophic factors A general term for molecules that promote the growth and survival of neurons.

neurotrophic hypothesis The idea that developing neurons compete for a limited supply of trophic factors secreted by their targets.

neurotrophins A family of trophic factor molecules that promote the growth and survival of several different classes of neurons.

neurula The early vertebrate embryo during the stage when the neural tube forms from the neural plate; follows the gastrula stage.

neurulation The process by which the neural plate folds to form the neural tube.

nociceptors Cutaneous and subcutaneous receptors (usually free nerve endings) specialized for the detection of harmful (noxious) stimuli.

nodes of Ranvier Periodic gaps in the myelination of axons where action potentials are generated.

non-rapid eye movement (non-REM) sleep Collectively, those phases of sleep characterized by the absence of rapid eye movements.

norepinephrine (noradrenaline) Catecholamine hormone and neurotransmitter that binds to α- and β-adrenergic receptors, both of which are G-protein-coupled receptors.

notochord A transient, cylindrical structure of mesodermal cells underlying the neural plate (and later the neural tube) in vertebrate embryos. Source of important inductive signals for spinal cord.

nucleus (plural, nuclei) Collection of nerve cells in the brain that are anatomically discrete, and which typically serve a particular function.

nucleus proprius Region of the dorsal horn of the spinal cord that receives information from nociceptors.

nystagmus Literally, a nodding movement. Refers to repetitive movements of the eyes normally elicited by large-scale movements of the visual field (optokinetic nystagmus). Nystagmus in the absence of appropriate stimuli usually indicates brainstem or cerebellar pathology.

occipital lobe The posterior lobe of the cerebral hemisphere; primarily devoted to vision.

ocular dominance columns The segregated termination patterns of thalamic inputs representing the two eyes in primary visual cortex of some mammalian species.

odorants Molecules capable of eliciting responses from receptors in the olfactory mucosa.

olfactory bulb Olfactory relay station that receives axons from cranial nerve I and transmits this information via the olfactory tract to higher centers.

olfactory epithelium Pseudostratified epithelium that contains olfactory receptor cells, supporting cells, and mucus-secreting glands.

olfactory receptor neurons Bipolar neurons in olfactory epithelium that contain receptors for odorants.

olfactory tracts see lateral olfactory tract.

oligodendrocytes One of three classes of central neuroglial cells; their major function is to elaborate myelin.

ontogeny The developmental history of an individual animal; also used as a synonym for development.

Onuf's nucleus Sexually dimorphic nucleus in the human spinal cord that innervates striated perineal muscles mediating contraction of the bladder in males, and vaginal constriction in females.

opioid Any natural or synthetic drug that has pharmacological actions similar to those of morphine.

opsins Proteins in photoreceptors that absorb light (in humans, rhodopsin and the three specialized cone opsins).

optic chiasm The junction of the two optic nerves on the ventral aspect of the diencephalon, where axons from the nasal parts of each retina cross the midline.

optic cup see optic vesicle.

optic disk The region of the retina where the axons of retinal ganglion cells exit to form the optic nerve.

optic nerve The nerve (cranial nerve II) containing the axons of retinal ganglion cells; extends from the eye to the optic chiasm.

optic radiation Portion of the internal capsule that comprises the axons of lateral geniculate neurons that carry visual information to the striate cortex.

optic tectum The first central station in the visual pathway of many vertebrates (analogous to the superior colliculus in mammals).

optic tract The axons of retinal ganglion cells after they have passed through the region of the optic chiasm en route to the lateral geniculate nucleus of the thalamus.

optic vesicle The evagination of the forebrain vesicle that generates the retina and induces lens formation in the overlying ectoderm.

optokinetic eye movements Movements of the eyes that compensate for head movements; the stimulus for optokinetic movements is large-scale motion of the visual field.

optokinetic nystagmus Repeated reflexive responses of the eyes to ongoing large-scale movements of the visual scene.

orbital (and medial prefrontal) cortex Division of the prefrontal cortex that lies above the orbits in the most rostral and ventral extension of the sagittal fissure; important in emotional processing and rational decision-making.

order A taxonomic category subordinate to class; comprises animal families.

orientation selectivity A property of many neurons in visual cortex in which they respond to edges presented over a narrow range of orientations.

oscillopsia An inability to fixate visual targets while the head is moving as a result of vestibular damage.

ossicles The bones of the middle ear

otoconia The calcium carbonate crystals that rest on the otolithic membrane overlying the hair cells of the sacculus and utricle.

otolithic membrane The gelatinous membrane on which the otoconia lie and in which the tips of the hair bundles are embedded.

otoliths Dense calcific structures (literally "ear stones"); important in generating the vestibular signals pertinent to balance.

outer segment Portion of photoreceptors made up of membranous disks that contain the photopigment responsible for initiating phototransduction.

oval window Site where the middle ear ossicles transfer vibrational energy to the cochlea.

overshoot The peak, positive-going phase of an action potential, caused by high membrane permeability to a cation such as Na^+ or Ca^{2+}.

oxytocin A 9-amino-acid neuropeptide that is both a putative neurotransmitter and a neurohormone.

Pacinian corpuscle Encapsulated mechanosensory receptor specialized for the detection of high-frequency vibrations.

Papez's circuit System of interconnected brain structures (mainly cingulate gyrus, hippocampus, and hypothalamus) in the medial aspect of the telencephalon and diencephalon described by James Papez. Participates in emotional processing, short-term declarative memory, and autonomic functions.

paracrine Term referring to the secretion of hormone-like agents whose effects are mediated locally rather than by the general circulation.

parallel fibers The bifurcated axons of cerebellar granule cells that synapse on dendritic spines of Purkinje cells.

paralysis Complete loss of voluntary motor control.

paramedian pontine reticular formation (PPRF) Neurons in the reticular formation of the pons that coordinate the actions of motor neurons in the abducens and oculomotor nuclei to generate horizontal movements of the eyes; also known as the "horizontal gaze center."

parasympathetic nervous system A division of the visceral motor system in which the effectors are cholinergic ganglion cells located near target organs.

paresis Partial loss of voluntary motor control; weakness.

parietal lobe The lobe of the brain that lies between the frontal lobe anteriorly, and the occipital lobe posteriorly.

Parkinson's disease A neurodegenerative disease of the substantia nigra that results in a characteristic tremor at rest and a general paucity of movement.

parvocellular Referring to the component of the primary visual pathway specialized for the detection of detail and color; so named because of the relatively small cells involved.

passive current flow Current flow across neuronal membranes that does not entail the action potential mechanism.

patch clamp An extraordinarily sensitive voltage clamp method that permits the measurement of ionic currents flowing through individual ion channels.

periaqueductal gray matter Region of brainstem gray matter that contains, among others, nuclei associated with the modulation of pain perception.

perilymph The potassium-poor fluid that bathes the basal end of the cochlear hair cells.

perineurium The connective tissue that surrounds a nerve fascicle in a peripheral nerve.

peripheral nervous system All nerves and neurons that lie outside the brain and spinal cord.

permissive An influence during development that permits differentiation to occur but does not specifically instruct cell fate.

phasic Transient firing of action potentials in response to a prolonged stimulus; the opposite of tonic.

phenotype The visible (or otherwise discernible) characteristics of an animal that arise during development.

phenotypic sex The visible body characteristics associated with sexual behaviors.

phospholipase A2A G-protein-activated enzyme that hydrolizes membrane phospholipids at the inner leaflet of the plasma membrane to release fatty acids such as arachadonic acid.

phospholipase CA G-protein-activated enzyme that hydrolizes membrane phospholipids at the inner leaflet of the plasma membrane to release a diacylglycerol and an inositol phosphate such as inositol trisphosphate (IP_3).

photopic vision Vision at high light levels that is mediated entirely by cones.

phylogeny The evolutionary history of a species or other taxonomic category.

phylum A major division of the plant or animal kingdom that includes classes having a common ancestry.

pia mater The innermost of the three layers of the meninges, which is closely applied to the surface of the brain.

pigment epithelium Pigmented coat underlying the retina important in the normal turnover of photopigment in rods and cones.

pineal gland Midline neural structure lying on the dorsal surface of the midbrain; important in the control of circadian rhythms (and, incidentally, considered by Descartes to be the seat of the soul).

pinna A component of the external ear.

pituitary gland Endocrine structure comprising an anterior lobe made up of many different types of hormone-secreting cells, and a posterior lobe that secretes neuropeptides produced by neurons in the hypothalamus.

placebo An inert substance that when administered may, because of the circumstances, have physiological effects.

planum temporale Region on the superior surface of the temporal lobe posterior to Heschl's gyrus; notable because it is larger in the left hemisphere in about two-thirds of humans.

plasticity Term that refers to structural or functional changes in the nervous system.

polarity Referring to a continually graded organization along one of the major axes of an animal.

polymodal Responding to more than one sensory modality.

polyneuronal innervation A state in which neurons or muscle fibers receive synaptic inputs from multiple, rather than single, axons.

pons One of the three components of the brainstem, lying between the midbrain rostrally and the medulla caudally.

pontine-geniculate-occipital (PGO) waves Characteristic encephalographic waves that signal the onset of rapid eye movement sleep.

pontine relay nuclei Collections of neurons in the pons that receive input from the cerebral cortex and send their axons across the midline to the cerebellar cortex via the middle cerebellar peduncle.

pore A structural feature of membrane ion channels that allows ions to diffuse through the channel.

pore loop An extracellular domain of amino acids, found in certain ion channels, that lines the channel pore and allows only certain ions to pass.

postcentral gyrus The gyrus that lies just posterior to the central sulcus; contains the primary somatic sensory cortex.

posterior Toward the back; sometimes used as a synonym for caudal or dorsal.

postganglionic Referring to axons that link visceral motor neurons in autonomic ganglia to their targets.

postsynaptic current (PSC) The current produced in a postsynaptic neuron by the binding of neurotransmitter released from a presynaptic neuron.

postsynaptic Referring to the component of a synapse specialized for transmitter reception; downstream at a synapse.

postsynaptic potential (PSP) The potential change produced in a postsynaptic neuron by the binding of neurotransmitter released from a presynaptic neuron.

post-tetanic potentiation (PTP) An enhancement of synaptic transmission resulting from high-frequency trains of action potentials.

precentral gyrus The gyrus that lies just anterior to the central sulcus; contains the primary motor cortex.

prefrontal cortex Cortical regions in the frontal lobe that are anterior to the primary and association motor cortices; thought to be involved in planning complex cognitive behaviors and in the expression of personality and appropriate social behavior.

preganglionic Referring to neurons and axons that link visceral motor neurons in spinal cord and brainstem to autonomic ganglia.

premotor cortex Motor association areas in the frontal lobe anterior to primary motor cortex; thought to be involved in planning or programming of voluntary movements.

pre-proproteins The first protein translation products synthesized in a cell. These polypeptides are usually much larger than the final, mature peptide, and often contain signal sequences that target the peptide to the lumen of the endoplasmic reticulum.

presynaptic Referring to the component of a synapse specialized for transmitter release; upstream at a synapse.

pretectum A group of nuclei located at the junction of the thalamus and the midbrain; these nuclei are important in the pupillary light reflex, relaying information from the retina to the Edinger-Westphal nucleus.

prevertebral (prevertebral ganglia) Sympathetic ganglia that lie anterior to the spinal column (distinct from the sympathetic chain ganglia).

primary auditory cortex The major cortical target of the neurons in the medial geniculate nucleus.

primary motor cortex A major source of descending projections to motor neurons in the the spinal cord and cranial nerve nuclei; located in the precentral gyrus (Brodmann's area 4) and essential for the voluntary control of movement.

primary neuron A neuron that directly links muscles, glands, and sense organs to the central nervous system.

primary sensory cortex Any one of several cortical areas receiving the thalamic input for a particular sensory modality.

primary visual cortex see striate cortex.

primary visual pathway (retinogenticulocortical pathway) Pathway from the retina via the lateral genticulate nucleus of the thalamus to the primary visual cortex; carries the information that allows conscious visual perception.

primate An order of mammals that includes lemurs, tarsiers, marmosets, monkeys, apes, and humans (technically, a member of this order).

priming A phenomenon in which the memory of an initial exposure is expressed unconsciously by improved performance at a later time.

primitive pit The thickened anterior end of the primitive streak; an important source of inductive signals during early development.

primitive streak Axial thickening in the ectoderm of the gastrulas of reptiles, birds, and mammals; the mesoderm forms by the ingression of cells at this site.

procedural memory Unconscious memories such as motor skills and associations.

production aphasia Aphasia that derives from cortical damage to those centers concerned with the motor aspects of speech.

promoter DNA sequence (usually within 35 nucleotides upstream of the start site of transcription) to which the RNA polymerase and its associated factors bind to initiate transcription.

proproteins Partially processed forms of proteins containing peptide sequences that play a role in the correct folding of the final protein.

proprioceptors Sensory receptors (usually limited to mechanosensory receptors) that sense the internal forces acting on the body; muscle spindles and Golgi tendon organs are the preeminent examples.

prosencephalon The part of the brain that includes the diencephalon and telencephalon (derived from the embryonic forebrain vesicle).

prosody (adjective, prosodic) The emotional tone or quality of speech.

prosopagnosia The inability to recognize faces; usually associated with lesions to the right inferior temporal cortex.

proteoglycan Molecule consisting of a core protein to which one or more long, linear carbohydrate chains (glycosaminoglycans) are attached.

proximal Closer to a point of reference (the opposite of distal).

psychotropic Referring to drugs that alter behavior, mood, and perception.

pulvinar A thalamic nucleus that receives its major input from sensory and association cortices and projects in turn to association cortices, particularly in the parietal lobe.

pupil The perforation in the iris that allows light to enter the eye.

pupillary light reflex The decrease in the diameter of the pupil that follows stimulation of the retina.

Purkinje cell The large principal projection neuron of the cerebellar cortex that has as its defining characteristic an elaborate apical dendrite.

putamen One of the three major nuclei that make up the basal ganglia.

pyramidal tract White matter tract that lies on the ventral surface of the medulla and contains axons descending from motor cortex to the spinal cord.

pyriform cortex Component of cerebral cortex in the temporal lobe pertinent to olfaction; so named because of its pearlike shape.

radial glia Glial cells that contact both the luminal and pial surfaces of the neural tube, providing a substrate for neuronal migration.

ramus Branch; typically applied to the white and gray communicating rami that carry visceral motor axons to the segmental nerves.

raphe nuclei A collection of serotonergic nuclei in the brainstem tegmentum; important in the governance of sleep and waking.

rapid eye movement (REM) sleep Phase of sleep characterized by low-voltage, high-frequency electroencephalographic activity accompanied by rapid eye movements.

receptive field Region of a receptor surface (e.g., the body surface or the retina) that causes a sensory nerve cell (or axon) to respond.

receptor A molecule specialized to bind any one of a large number of chemical signals, preeminently neurotransmitters.

receptor neuron A neuron specialized for the transduction of energy in the environment into electrical signals.

receptor potential The membrane potential change elicited in receptor neurons during sensory transduction.

5-α-reductase Enzyme that converts testosterone to dihydrotestosterone.

reflex A stereotyped (involuntary) motor response elicited by a defined stimulus.

refractory period The brief period after the generation of an action potential during which a second action potential is difficult or impossible to elicit.

remodeling Change in the anatomical arrangement of neural connections.

reserpine An antihypertensive drug that is no longer used due to side effects such as behavioral depression.

resting potential The inside-negative electrical potential that is normally recorded across all cell membranes.

reticular activating system Region in the brainstem tegmentum that, when stimulated, causes arousal; involved in modulating sleep and wakefulness.

reticular formation A network of neurons and axons that occupies the core of the brainstem, giving it a reticulated appearance in myelin-stained material; major functions include control of respiration and heart rate, posture, and state of consciousness.

retina Laminated neural component of the eye that contains the photoreceptors (rods and cones) and the initial processing machinery for the primary (and other) visual pathways.

retinoic acid A derivative of vitamin A that acts as an inducer during early brain development.

retinotectal system The pathway between ganglion cells in the retina and the optic tectum of vertebrates.

retrograde A movement or influence acting from the axon terminal toward the cell body.

reversal potential The membrane potential of a post-synaptic neuron (or other target cell) at which the action of a given neurotransmitter causes no net current flow.

rhodopsin The photopigment found in rods.

rhombencephalon The part of the brain that includes the pons, cerebellum, and medulla (derived from the embryonic hindbrain vesicle).

rhombomere Segment of the developing rhombencephalon.

rising phase The initial, depolarizing, phase of an action potential, caused by the regenerative, voltage-dependent influx of a cation such as Na^+ or Ca^{2+}.

rods Photoreceptors specialized for operating at low light levels.

rostral Anterior, or "headward."

rostral interstitial nucleus Neurons in the midbrain reticular formation that coordinate the actions of neurons in the oculomotor nuclei to generate vertical movements of the eye; also known as the "vertical gaze center."

saccades Ballistic, conjugate eye movements that change the point of foveal fixation.

sacculus The otolith organ that detects linear accelerations and head tilts in the vertical plane.

sagittal Referring to the anterior-posterior plane of an animal.

saltatory conduction Mechanism of action potential propagation in myelinated axons; so named because action potentials "jump" from one node of Ranvier to the next due to generation of action potentials only at these sites.

Scarpa's ganglion The ganglion containing the bipolar cells that innervate the semicircular canals and otolith organs.

Schaffer collaterals The axons of cells in the CA3 region of hippocampus that form synapses in the CA1 region.

Schwann cells Neuroglial cells in the peripheral nervous system that elaborate myelin (named after the nineteenth-century anatomist and physiologist Theodor Schwann).

sclera The external connective tissue coat of the eyeball.

scotoma A defect in the visual field as a result of pathological changes in some component of the primary visual pathway.

scotopic Referring to vision in dim light, where the rods are the operative receptors.

second-order neurons Projection neurons in a sensory pathway that lie between the primary receptor neurons and the third-order neurons.

segment One of a series of more or less similar anterior-posterior units that make up segmental animals.

segmentation The anterior-posterior division of animals into roughly similar repeating units.

semaphorins A family of diffusible, growth-inhibiting molecules (see also collapsin).

semicircular canals The vestibular end organs within the inner ear that sense rotational accelerations of the head.

sensitization Increased sensitivity to stimuli in an area surrounding an injury. Also, a generalized aversive response to an otherwise benign stimulus when it is paired with a noxious stimulus.

sensorineural hearing loss Diminished sense of hearing due to damage of the inner ear or its related central auditory structures. Contrast with conductive hearing loss.

sensory Pertaining to sensation.

sensory aphasia Difficulty in communicating with language that derives from cortical damage to those areas concerned with the comprehension of speech.

sensory ganglia see dorsal root ganglia.

sensory system Term sometimes used to describe all the components of the central and peripheral nervous system concerned with sensation.

sensory transduction Process by which energy in the environment is converted into electrical signals by sensory receptors.

serotonin A biogenic amine neurotransmitter derived from the amino acid tryptophan.

sexually dimorphic Having two different forms depending on genotypic or phenotypic sex.

short-term memory Memories that last from seconds to minutes.

silver stain A classical method for visualizing neurons and their processes by impregnation with silver salts (the best-known technique is the Golgi stain, developed by the Italian anatomist Camillo Golgi in the late nineteenth century).

size principle The orderly recruitment of motor neurons by size to generate increasing amounts of muscle tension.

sleep spindles Bursts of electroencephalographic activity, at a frequency about 10–14 Hz and lasting a few seconds; spindles characterize the initial descent into non-REM sleep.

small molecule neurotransmitters Referring to the non-peptide neurotransmitters such as acetylcholine, the amino acids glutamate, aspartate, GABA, and glycine, as well as the biogenic amines.

smooth pursuit eye movements Slow, tracking movements of the eyes designed to keep a moving object aligned with the fovea.

soma (plural, somata) The cell body.

somatic cells Referring to the cells of an animal other than its germ cells.

somatic sensory cortex That region of the cerebral cortex concerned with processing sensory information from the body surface, subcutaneous tissues, muscles, and joints; located primarily in the posterior bank of the central sulcus and on the postcentral gyrus.

somatic sensory system Components of the nervous system involved in processing sensory information about the mechanical forces active on both the body surface and on deeper structures such as muscles and joints.

somatotopic maps Cortical or subcortical arrangements of sensory pathways that reflect the organization of the body.

somites Segmentally arranged masses of mesoderm that lie alongside the neural tube and give rise to skeletal muscle, vertebrae, and dermis.

species A taxonomic category subordinate to genus; members of a species are defined by extensive similarities, including the ability to interbreed.

specificity Term applied to neural connections that entail specific choices between neurons and their targets.

spina bifida A congenital defect in which the neural tube fails to close at its posterior end.

spinal cord The portion of the central nervous system that extends from the lower end of the brainstem (the medulla) to the cauda equina.

spinal ganglia see dorsal root ganglia.

spinal nucleus of the bulbocavernosus Sexually dimorphic collection of neurons in the lumbar region of the rodent spinal cord that innervate striated perineal muscles.

spinal shock The initial flaccid paralysis that accompanies damage to descending motor pathways.

spinal trigeminal tract Brainstem tract carrying fibers from the trigeminal nerve to the spinal nucleus of the trigeminal complex (which serves as the relay for painful stimulation of the face).

spinocerebellum Region of the cerebellar cortex that receives input from the spinal cord, particularly Clarke's column in the thoracic spinal cord.

spinothalamic pathway see anterolateral pathway.

spinothalamic tract Ascending white matter tract carrying information about pain and temperature from the spinal cord to the VP nuclear complex in the thalamus; also referred to as the anterolateral tract.

split-brain patients Individuals who have had the cerebral commissures divided in the midline to control epileptic seizures.

sporadic Cases of a disease that apparently occur at random in a population; contrasts with familial or inherited.

stem cells Undifferentiated cells from which other cells, including neurons, can be derived.

stereocilia The actin-rich processes that, along with the kinocilium, form the hair bundle extending from the apical surface of the hair cell; site of mechanotransduction.

stereopsis The perception of depth that results from the fact that the two eyes view the world from slightly different angles.

strabismus Developmental misalignment of the two eyes; may lead to binocular vision being compromised.

stria vascularis Specialized epithelium lining the cochlear duct that maintains the high potassium concentration of the endolymph.

striate cortex Primary visual cortex in the occipital lobe (also called Brodmann's area 17). So named because the prominence of layer IV in myelin-stained sections gives this region a striped appearance.

striatum (neostriatum) see corpus striatum.

striola A line found in both the sacculus and utricle that divides the hair cells into two populations with opposing hair bundle polarities.

subarachnoid space The cerebrospinal fluid—filled space over the surface of the brain that lies between the arachnoid and the pia.

substance P An 11-amino acid neuropeptide; the first neuropeptide to be characterized.

substantia nigra Nucleus at the base of the midbrain that receives input from a number of cortical and subcortical structures. The dopaminergic cells of the substantia nigra send their output to the caudate/putamen, while the GABAergic cells send their output to the thalamus.

subthalamic nucleus A nucleus in the ventral diencephalon that receives input from the caudate/putamen and participates in the modulation of motor behavior.

sulci (singular, sulcus) The infoldings of the cerebral hemisphere that form the valleys between the gyral ridges.

summation The addition in space and time of sequential synaptic potentials to generate a larger than normal postsynaptic response.

superior colliculus Laminated structure that forms part of the roof of the midbrain; plays an important role in orienting movements of the head and eyes.

suprachiasmatic nucleus Hypothalamic nucleus lying just above the optic chiasm that receives direct input from the retina; involved in light entrainment of circadian rhythms.

Sylvian fissure see lateral fissure.

sympathetic nervous system A division of the visceral motor system in vertebrates comprising, for the most part, adrenergic ganglion cells located relatively far from the related end organs.

synapse Specialized apposition between a neuron and its target cell for transmission of information by release and reception of a chemical transmitter agent.

synaptic cleft The space that separates pre- and postsynaptic neurons at chemical synapses.

synaptic depression A short-term decrease in synaptic strength resulting from the depletion of synaptic vesicles at active synapses.

synaptic vesicle recycling A sequence of budding and fusion reactions that occurs within presynaptic terminals to maintain the supply of synaptic vesicles.

synaptic vesicles Spherical, membrane-bound organelles in presynaptic terminals that store neurotransmitters.

syncytium A group of cells in protoplasmic continuity.

target (neural target) The object of innervation, which can be either non-neuronal targets, such as muscles, glands, and sense organs, or other neurons.

taste buds Onion-shaped structures in the mouth and pharynx that contain taste cells.

tectorial membrane The fibrous sheet overlying the apical surface of the cochlear hair cells; produces a shearing motion of the stereocilia when the basilar membrane is displaced.

tectum A general term referring to the dorsal region of the brainstem (tectum means "roof").

tegmentum A general term that refers to the central gray matter of the brainstem.

telencephalon The part of the brain derived from the anterior part of the embryonic forebrain vesicle; includes the cerebral hemispheres.

temporal (temporal division) Referring to the region of the visual field of each eye in the direction of the temple.

temporal lobe The hemispheric lobe that lies inferior to the lateral fissure.

terminal A presynaptic (axonal) ending.

tetraethylammonium A quaternary ammonium compound that selectively blocks voltage-sensitive K^+ channels; eliminates the delayed K^+ current measured in voltage clamp experiments.

tetrodotoxin An alkaloid neurotoxin, produced by certain puffer fish, tropical frogs, and salamanders, that selectively blocks voltage-sensitive Na^+ channels; eliminates the initial Na^+ current measured in voltage clamp experiments.

thalamus A collection of nuclei that forms the major component of the diencephalon. Although its functions are many, a primary role of the thalamus is to relay sensory information from lower centers to the cerebral cortex.

thermoreceptors Receptors specialized to transduce changes in temperature.

threshold The level of membrane potential at which an action potential is generated.

tight junction A specialized junction between epithelial cells that seals them together, preventing most molecules from passing across the cell sheet.

tip links The filamentous structures that link the tips of adjacent stereocilia; thought to mediate the gating of the hair cell's transduction channels.

tonic Sustained activity in response to an ongoing stimulus; the opposite of phasic.

tonotopy the topographic mapping of frequency across the surface of a structure, which originates in the cochlea and is preserved in ascending auditory structures, including the auditory cortex.

transcription factors A general term applied to proteins that regulate transcription, including basal transcription factors that interact with the RNA polymerase to initiate transcription, as well as those that bind elsewhere to stimulate or repress transcription.

transcriptional activator proteins Proteins that bind DNA and activate the transcription of DNA.

transducin G-protein involved in the phototransduction cascade.

transduction see sensory transduction.

transforming growth factor (TGF) A class of peptide growth factors that acts as an inducer during early development.

transgenderism Gender identification with the opposite phenotypic sex.

transmitter see neurotransmitter.

transporters (active transporters) Cell membrane molecules that consume energy to move ions up their concentration gradients, thus restoring and/or maintaining normal concentration gradients across cell membranes.

trichomatic Referring to the presence of three different cone types in the human retina, which generate the initial steps in color vision by differentially absorbing long, medium, and short wavelength light.

tricyclic antidepressants A class of antidepressant drugs named for their three-ringed molecular structure; thought to act by blocking the reuptake of biogenic amines.

trigeminal ganglion The sensory ganglion associated with the trigeminal nerve (cranial nerve V).

Trk receptors The receptors for the neurotrophin family of growth factors.

trophic The ability of one tissue or cell to support another; usually applied to long-term interactions between pre- and postsynaptic cells.

trophic factor (agent) A molecule that mediates trophic interactions.

trophic interactions Referring to the long-term interdependence of nerve cells and their targets.

trophic molecules see trophic factor.

tropic An influence of one cell or tissue on the direction of movement (or outgrowth) of another.

tropic molecules Molecules that influence the direction of growth or movement.

tropism Orientation of growth in response to an external stimulus.

tuning curve Referring to a common physiological test in which the receptive field properties of neurons are gauged against a varying stimulus such that maximum sensitivity or maximum responsiveness can be defined by the peak of the tuning curve.

tympanic membrane The eardrum.

undershoot The final, hyperpolarizing phase of an action potential, typically caused by the voltage-dependent efflux of a cation such as K^+.

upper motor neuron A neuron that gives rise to a descending projection that controls the activity of lower motor neurons in the brainstem and spinal cord.

upper motor neuron syndrome Signs and symptoms that result from damage to descending motor systems; these include paralysis, spasticity, and a positive Babinski sign.

utricle The otolith organ that senses linear accelerations and head tilts in the horizontal plane.

vasopressin A 9-amino-acid neuropeptide that acts as a neurotransmitter, as well as a neurohormone.

ventral Referring to the belly; the opposite of dorsal.

ventral horn The ventral portion of the spinal cord gray matter; contains the primary motor neurons.

ventral posterior complex Group of thalamic nuclei that receives the somatic sensory projections from the dorsal column nuclei and the trigeminal nuclear complex.

ventral posterior lateral nucleus Component of the ventral posterior complex of thalamic nuclei that receives brainstem projections carrying somatic sensory information from the body (excluding the face).

ventral posterior medial nucleus Component of the ventral posterior complex of thalamic nuclei that receives brainstem projections related to somatic sensory information from the face.

ventral roots The collection of nerve fibers containing motor axons that exit ventrally from the spinal cord and contribute the motor component of each segmental spinal nerve.

ventricles The fluid-filled spaces in the vertebrate brain that represent the lumen of the embryonic neural tube.

ventricular zone The sheet of cells closest to the ventricles in the developing neural tube.

vergence movements Disjunctive movements of the eyes (convergence or divergence) that align the fovea of each eye with targets located at different distances from the observer.

vertebrate An animal with a backbone (technically, a member of the subphylum Vertebrata).

vesicle Literally, a small sac. Used to refer to the organelles that store and release transmitter at nerve endings. Also used to refer to any of the three dilations of the anterior end of the neural tube that give rise to the three major subdivisions of the brain.

vestibulocerebellum The part of the cerebellar cortex that receives direct input from the vestibular nuclei or vestibular nerve.

vestibulo-ocular reflex Involuntary movement of the eyes in response to displacement of the head. This reflex allows retinal images to remain stable while the head is moved.

visceral (noun, viscera) Referring to the internal organs of the body cavity.

visceral motor system The component of the motor system (also known as the autonomic nervous system) that motivates and governs visceral motor behavior.

visceral nervous system Synonymous with autonomic nervous system.

visual field The area in the external world normally seen by one or both eyes (referred to, respectively, as the monocular and visual binocular fields).

vital dye A reagent that stains cells when they are alive.

voltage clamp A method that uses electronic feedback to control the membrane potential of a cell, simultaneously measuring transmembrane currents that result from the opening and closing of ion channels.

voltage-gated Term used to describe ion channels whose opening and closing is sensitive to membrane potential.

Wallerian degeneration The process by which the distal portion of a damaged axon segment degenerates; named after Augustus Waller, a nineteenth-century physician and neuroanatomist.

Wernicke's aphasia Difficulty comprehending speech as a result of damage to Wernicke's language area.

Wernicke's area Region of cortex in the superior and posterior region of the left temporal lobe that helps mediate language comprehension. Named after the nineteenth-century neurologist, Carl Wernicke.

white matter A general term that refers to large axon tracts in the brain and spinal cord; the phrase derives from the fact that axonal tracts have a whitish cast when viewed in the freshly cut material.

working memory Memories held briefly in mind that enable a particular task to be accomplished (e.g., efficiently searching a room for a lost object).

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